Focus on Sexuality Research

Series Editor: Marta Meana

Baudewijntje P.C. Kreukels
Thomas D. Steensma
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Gender Dysphoria and Disorders of Sex Development

Progress in Care and Knowledge

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To Peggy Cohen-Kettenis:
A pioneer in the fields of Gender Dysphoria
and Disorders of Sex Development

Preface

After several decades of invaluable work in the field of Gender Dysphoria (GD) and Disorders of Sex Development (DSD), Prof. Dr. Peggy Cohen-Kettenis will retire in 2013. Starting her work with individuals with GD and DSD in 1987, Peggy Cohen-Kettenis became a scientific leader in the field by publishing numerous papers over the years. She was a pioneer through her involvement in the development on the "Dutch Protocol," on the treatment of adolescents with GD, in her participation in several guidelines on the treatment of individuals with GD and DSD, and as chair of the American Psychiatric Association's DSM-V subworkgroup on Gender Identity Disorders. At the moment, she is a member of the ICD-11 working group on Sexual Disorders and Sexual Health.

We have asked a number of people who worked closely with Peggy to describe her career: her promoter during her PhD period, Prof. Dr. W.T.A.M. Everaerd; one of her PhD students in Utrecht, Prof. Dr. J.T. Swaab; the former director of the Genderteam at VU University Medical Center, Prof. Dr. L.J. Gooren and the coordinator of the Genderteam at VU University Medical Center, J. Megens; and the director of the Center of Expertise on Gender Dysphoria at VU University Medical Center, Dr. M.A.A. van Trotsenburg.

The ICIP in Utrecht

On August 23, 1948, Peggy was born in Djakarta. To place this in historical perspective, on August 30 the Radio Philharmonic Orchestra performed their opening concert in the Garden Hall at the zoo of what then was still called Batavia. In the announcement of the *Nederlands muziekinstituut* (http://www.nederlandsmuziekinstituut.nl), it was announced that the Dutch government planned to engage a group of musicians for 2 years to form a radio orchestra. *"Because in the East it is still not safe, which implied that it was a risky mission. Anyway, 'overseas' in those years* *there was a great need for cultural facilities."* The members of the orchestra returned to the Netherlands in 1950 with the M.S. Johan van Oldenbarnevelt. Peggy may not have been aware of this celebratory concert near her birthday, but it is nice that there was already music for her.

In 1968, the *revolution year*, she went to Utrecht University to study clinical and developmental psychology. She graduated in 1973, but already had a good working relationship with the behavior therapy group at the Department of Clinical Psychology (the ICIP). She became a behavior therapist and supervisor of trainees in behavior therapy, and somewhat later she continued her psychotherapy education at the Institute of Medical Psychotherapy.

Behavior therapy was introduced in the Netherlands in the early 1960s. We initiated a group "Behavior therapy and behavior modification." Initially, we focused on teaching behavior therapy, which was soon followed by the development of a research plan. ZWO (Pure Scientific Research), currently the Netherlands Organization for Scientific Research (NWO), in those years supported a strong group of psychonomic psychologists. By 1970, social psychologists and clinical psychologists had merged with the psychonomic group into the foundation Psychon. At this time, it became easier to apply for grants for clinical studies, particularly for studies with an experimental approach and design. In 1970 we obtained a grant for "Behavioral treatment of agoraphobia," then in 1972 for "Social skills training," and the third in 1975 for "The development of phobias." Peggy planned to look into the tendency of children to react anxiously as a function of perceived causal relationships between events, especially whether they could exert control over the events. In the meantime, we learned that in Amsterdam Erie Fournier and Yara Dekking had a plan to study social anxiety. The plan was supported by a grant of the *Preventie Fonds*. Bringing these plans together could lead to a fruitful cooperation, and it thus went forward. Peggy would take the task to construct measures for cognitive aspects and Yara did the same for social anxiety. When the measures were available, it would be possible to study the cognitive aspects of social anxiety. Cognitive aspects of social anxiety in children also became the title of the combined dissertation, which appeared in 1980.

In 1973, I became involved in problems concerning transsexuality. Together with Lex van Naerssen, we had built a relationship with working groups of the Netherlands Society for Sexual Reform (NVSH). We offered assistance to people who experienced problems with their sexual preferences. Sometimes people were troubled by their contacts with law enforcers, e.g., because they exposed themselves as exhibitionists. We also supported working groups, especially the work group transvestite and transsexuality. We became acquainted with Anton Verschoor who was very active in the NVSH and in the Foundation Netherlands Gender Centre. In 1973, the Health Council of the Netherlands set up a committee for a renewed consideration, after the negative findings and advice of a 1965 committee on the treatment of people with gender dysphoria and the legal adjustment of sex determination. Anton Verschoor wrote about the situation after 1965: "In professional circles there exists significant disagreement about the origins of the phenomenon of transsexuality; a majority of the psychiatrists consider these people as serious patients and on this ground they oppose and reject somatic interventions. The operations were not considered to be a medical necessity and therefore are not to be paid for by the medical assurance boards." Verschoor also writes: "Or, recently: is it proper and responsible that such an individual meets with his children on a regular basis; would that burden the child with identity problems?" (Verschoor, 1983). In 1974 the Supreme Court of the Netherlands announced that it was no longer possible to change birth certificates.

All members of the 1973 committee knew people who suffered from gender dysphoria, and, in contrast with the 1965 committee, they were positive about hormonal and surgical interventions and they also argued for the adjustment of the birth certificate. The *transsexism* committee took its name from a proposal by committee member Coen van Emde Boas, who reasoned that gender dysphoria is about sex (determination) and not about sexuality, thus transsexism. He was an important advocate for treatment. Legal issues were in the hands of Frans van der Reijt, lawyer and committee member. The committee noted that there was no reported scientific evidence about the efficacy of the treatment of gender dysphoria. There was also no systematic review in which treatment probands (those who ask treatment for gender dysphoria) had received treatments.

As a member of the committee, I was invited to design a study among probands who had been treated for gender dysphoria. About that time, Peggy was finishing her dissertation work, and she already had become a member of what we called the working group on the sexuality project. In 1977, together with Lex van Naerssen, we wrote a book about sexuality. Peggy also became active as a member of the board of Netherland's Society of Sexology. In 1979–1980 we wrote a grant application, which was funded by ZWO-Psychon for the "Ex-post facto evaluation of the treatment of transsexualism." Peggy acted as direct and daily supervisor of Abraham (Bram) Kuiper who performed the research as part of his dissertation. The study was conducted in close cooperation with Louis Gooren's group, currently well known under the name of "Kennis- en Zorgcentrum voor Genderdysforie" at VUmc. Bram obtained his doctoral degree in 1991. In 1987, Peggy moved to Utrecht Medical School and in 2002 to VUmc. Late in 1985, I moved to the University of Amsterdam.

It has never been difficult to follow Peggy's work. She is an international expert on gender dysphoria and eventually became director of the Kennis- en Zorgcentrum at VUmc.

Walter Everaerd

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Peggy at the University Medical Centre Utrecht (1987–2002)

In 1987 Peggy became associate professor at the University Medical Centre Utrecht (UMCU), in the Department of Child and Adolescent Psychiatry. The UMCU was called the Academic Hospital Utrecht at that time, and the Child and Adolescent Psychiatry unit was situated in the center of Utrecht, in Nicolaas Beetsstraat at a time when we all went out for lunch in the center of the city. Peggy's room was in the cozy attic of the outpatient child and adolescent clinic, where the child psychiatrists and psychologists had their offices. During that time, new hospital and university buildings were prepared in Uithof, outside of the city. A few years later, we moved with the adolescent clinics from Nicolaas Beetsstraat to a temporary location of "Geertebolwerk," to wait for our new location, which would be ready for use in 1989. The old charming location was redesigned as housing for young urban professionals.

The Department of Child and Adolescent Psychiatry of the University Medical Centre of Utrecht consisted of age-specific outpatient divisions (infants, children, and adolescents), several inpatient units, and a unit for acute psychiatric problems where adolescents with the first psychotic episodes were taken care of. Each subdepartment of child and adolescent psychiatry was headed by a child psychiatrist who was responsible for the quality of the patient care and to whom the personnel had to report. According to a matrix structure of management, Peggy headed the psychologists and educationists of all subdepartments of the Child and Adolescent Psychiatry. Consequently, she was part of the management team of the Department of Child and Adolescent Psychiatry. Right after she arrived in UMCU, Peggy started frequent meetings of psychologists and educationists to synchronize assessment procedures and to introduce systematic updates of evidence-based methods of assessment and treatment. She introduced a positive, critical, and innovative climate within the group. As a result, the group was ready for education of students and young professionals that were following post-master tracks for psychotherapy and clinical psychology. Moreover, she stimulated research projects within the group that involved assessment and treatment. Being an academic specialized department with a supraregional function, child and adolescent psychiatry focused on serious psychopathology with high impact on quality of life. The specific regions of interest were neurodevelopmental disorders, mainly addressed from a neurobiological perspective, under the inspiring and stimulating management of Prof. Dr. Herman van Engeland. The Department of Child and Adolescent Psychiatry became part of the "brain division" of UMCU (psychiatry, neurology, sports medicine, and rehabilitation medicine); Peggy divided her growing group of psychologists and educationists into three sections, with specific expertise on (1) assessment, (2) individual and group therapy, and (3) family therapy. These sections participated in the continuous education of child psychiatrists and psychologists. Many health psychologists, psychotherapists, and clinical psychologists were trained to meet the requirements for certification.

In the highly specialized Department of Child and Adolescent Psychiatry, several lines of research were combined with high standards of care: The focus was on autism spectrum disorders, psychosis, behavioral disorders, anxiety disorders, eating disorders, psychosomatic disorders, and gender identity disorders. Not surprisingly, Peggy was the one who was leading in the development of the care for children and adolescents with gender identity disorders. She instructed students and young professionals in the gender identity interview, taught us to observe specific aspects of gender development in children and adolescents, and started multidisciplinary consulting hours for children and adolescents with gender dysphoria. We, the junior colleagues, were trained in assessment and treatment of these youngsters in individual therapy as well as in groups.

Peggy expanded her work to Wilhelmina Children's Hospital (part of UMCU) and participated in the team for gender disturbances. The team consisted of pediatricians, clinical geneticists, urologists, endocrinologists, child surgeons, and psychologists. The team took care of children who were born with undefined gender or children with problems in gender development, e.g., due to androgen insensitivity syndrome. These children and their parents were psychologically treated by Peggy for years. In this team, children with genetic syndromes with consequences for gender development and their parents were also treated and guided, like boys with "Klinefelter syndrome" (47,XXY) and girls with "triple X" (47,XXX) or "Turner syndrome" (45,X0). This team was highly specialized in medical and psychological treatment of complex gender problems in children, and its reputation resulted in admission of patients from all over the world.

In 1993 Peggy was appointed special professor of gender development and psychopathology at the Medical Faculty in Utrecht. In 1996 she became the head of the department of medical psychology, organizing the psychological care for patients in all divisions of UMCU.

Peggy inspired many researchers and supervised many research projects. During the 15 years that she was appointed at UMCU, she supervised 12 PhD students, on the following research topics: "Developmental impact of neonatal stress" (Dr. P. F. Schothorst, 1990); "Transsexuality, evaluation of sex-change treatment" (Dr. A. J. Kuiper, 1991); "Prenatal exposure to Phenobarbital and diphantoin: A study on long-lasting consequences" (Dr. A. Dessens, 1996); "Towards a gender identity theory of transsexualism" (Dr. C. Doorn, 1997); "Information processing in a child psychiatric population" (Dr. H. Swaab, 1998); "Effects of sex hormones on cognition and emotion" (Dr. D. Slabbekoorn); "The effect of manualized behavior therapy with disruptive behavior disordered children in everyday clinical practice: A randomized clinical trial" (Dr. N. van de Wiel); "Sex reassignment. Predictors and outcome of treatment for transsexuals" (Dr. Y. Smith); "Emotional functioning in anorexia nervosa patients. A study on emotional experiences and neurophysiological responses" (Dr. M. de Zonnevylle); "Biological roots of sex differences: a longitudinal twin study" (Dr. C. Cohen-Bendahan); "Prenatal sex hormones and gender-related behavior" (Dr. C. van de Beek); and "Construction and validation of a questionnaire measuring social competence in youth" (Dr. E. Hulstijn). Many of her PhD students will remember Peggy's reassuring words in times of research stress: “Just remember that doing research is basically only about counting and summarizing!” She was a very active reviewer in her field of expertise in those years, and in the same period she managed to publish numerous papers in high-impact peer-reviewed journals. She also organized numerous symposia at national and international conferences and held innumerable lectures. In addition, Peggy has been a member of the national research program committee “Geestkracht” since 2001 (ZonMw) and a member of the group that took care of the education of researchers in the national mental health care (since 2001).

In the same period that she devoted so much attention to her innovative clinical work, her impressive management job, and her pioneering research, Peggy was also very active in the Dutch professional network of psychologists. She headed the large division of “individual health psychologists” of the Dutch Society of Psychology from 1997 to 2000. I remember her discussing the specific mission for professionals at that time. She gave much of her energy to the development of the national register of clinical psychologists, a large step forward for the Dutch community of psychologists. She took part in the national advisory committee for installation of psychological specialists in the Netherlands (“College article 14 professions”) from 2002 to 2005. She also was a member of the supervisory board of the Association of Behavioural and Cognitive Therapy (1992–1999), and she was the chair of the curriculum committee and the principal lecturer of the post-master therapy education track in the central regions of the Netherlands from 1999 to 2004. On behalf of the University of Utrecht and the UMCU, she was a board member of the “foundation of post-master education in mental health care” (PDO-GGZ); this foundation took responsibility for the quality of post-master education in the central regions of the Netherlands. Moreover, Peggy took part in the steering committee to supervise the development of national multidisciplinary protocols for mental health care from1999 to 2001.

During this period, Peggy also participated in the board of the Dutch society for Sexology (1994–2005) and in the board of the foundation of Medical Sexology (1993–2002). She has been a member of the board of the World Professional Association for Transgender Health (since 1995) and a member of the executive committee of the International Association for Child and Adolescent Psychiatry and Allied Disciplines (since 1999). In addition to all the above activities, from 1987 to 2002, Peggy participated in several project groups and committees to help develop the professional qualities of national and international psychologists.

Besides being an innovative clinician and researcher and a very inspiring and dedicated manager, Peggy also is a very pleasant colleague and wonderful person. On request, Prof. Dr. Herman van Engeland, the head of the department at that time, looked back at Peggy’s contribution to the Department of Child and Adolescent Psychiatry and praises her loyalty and reliability, her involvement with patients as well as colleagues, her enormous productivity, and her dedication to her work. She was a pleasant, quietly persistent, charming, and connected member of the staff who, on occasion, showed her excellent qualities as a cook by preparing very impressive Indonesian meals for her very grateful colleagues, whom she also traditionally offered Indonesian “spekkoek” on the occasion of her birthday.

Another member of the staff, Prof. Dr. Walter Matthys, at that time head of the clinic of behavioral disorders, remembers Peggy as "good-humored," "cheerful," "pragmatic," "swift," and "witty." Dr. Jacques Giltay, a clinical geneticist and member of the multidisciplinary team for gender disturbances, describes Peggy as a very friendly and accessible person. She was highly respected for her knowledge and skills. A very nice colleague, e.g., illustrated by the fact that she acknowledged the contribution of the complete gender team in a chapter that she was invited to write for a handbook. Dr. Maretha de Jonge, one of the members of her group of psychologists and educationists, characterizes Peggy as a "pioneering professional," a "warm person," and a "stylish professor," who was an "inspiring example" for young psychologists at the time.

Dr. Astrid Hoppe, a clinical psychologist in UMCU, values her open door policy: "Peggy was always available, not only as a manager, but also for personal issues." She welcomed us colleagues frequently in her home: "We enjoyed many fine Indonesian meals at Peggy's house." She was an example for us in multitasking: "She combined her professional ambition with family life, seemingly finding the right work-life balance." Peggy was able to put things in perspective: "Always positive and in control, I've never seen Peggy stressed." Dr. Karin Tobias, clinical psychologist in UMCU at that time, now living and working in Perth, Australia, adds: "Peggy was the founder of the section of clinical psychology, I always perceived her as a team player." "She was very dedicated to her patients and an advocate for better treatment for children and adolescents with Gender Identity Disorder." "Next to this, she loved Asian food, good wine and social activities."

Prof. Dr. Stephanie van Goozen, a fellow researcher in UMCU at that time, now appointed in Cardiff and Leiden, describes Peggy as "insightful," in terms of not only her thinking and science but also her clinical work; "composed," she never got agitated in times of stress, always remaining calm and collected, and dignified; and "enigmatic," as in mysterious and defying description, she is not an easy nut to crack!

Peggy was very much appreciated in UMCU, and she was a very dedicated and productive clinician and scientist, a skilled and inspiring manager and supervisor, and, above all, a great colleague!

Hanna Swaab

Peggy and the VUmc

Peggy Cohen-Kettenis started her research in the field of gender dysphoria with the first Dutch study evaluating the treatment of adult patients with gender identity conditions. This study was conducted at the initiative of the Dutch Health Council, published in 1979, and concluded that treatment of transsexual individuals brought relief from their suffering. This study provided the impetus for a new Dutch law allowing transsexual people to amend their birth certificates. From 1987 to 2002, she worked at the Department of Child and Adolescent Psychiatry of the University Medical Centre Utrecht. Here, she initiated the first clinic in Europe for children and adolescents with gender dysphoria and intersex conditions, as they were then known. The later description, Disorders of Sex Development, has not been well received by many who have these conditions, so in deference to them, I will use DSD to indicate "differences" of sex development.

There was an informal collaboration with the gender clinic at VU University Medical Center. Peggy's clinic actually moved to this center in 2002 and integrated with the gender clinic and thus became part of the larger Center of Expertise on Gender Dysphoria. At her transfer to the new workplace, she received promises of great support but, as is often the case, the reality was different. So, single-handedly, Peggy developed the field of gender dysphoria and widened the context in which it was understood, by considering gender identity issues alongside DSDs, especially those which are associated with ambiguous genital appearance at birth, thus acknowledging some parallels between these conditions, and the intricate influences of prenatal hormones on later gendered behavior and expression. Similarly, clinical and psychosocial aspects of care have common features in terms of gender assignment, information management and communication, timing of medical interventions, consequences of surgery, and sexuality. Although outcomes are generally satisfactory for children with DSDs, a variety of medical and psychosocial factors impinge on their psychological development, which may lead to a later need to adjust the gender role and status to achieve congruence with the gender identity.

The clinical management of gender dysphoria in individuals with DSDs has benefited from insights, and approaches to care, that have been developed for gender-dysphoric individuals who do not have genital anomalies. In the care of children with DSDs, neonatal clinical decisions are often made with long-lasting effects on quality of life. These decisions should, therefore, be based on empirical evidence. Yet, specific evidence regarding gender assignment, information management, and timing of surgery is only now starting to emerge. Peggy believed that these areas of study, as well as observations in gender-troubled children, would lead to a wider understanding of gender development in all human beings and would provide a useful basis for further studies in the field.

Peggy Cohen-Kettenis is a beautiful person, inside and out! Her amazing contribution to the health and well-being of transgender adults and young people owes much to her ability to build relationships, not only with patients and families, for whom she shows empathy and understanding, but also with her colleagues towards whom she is respectful and generous of spirit. Peggy's reputation is legendary; she is, for those of us who have had the privilege to work with her, quite simply, the best.

Peggy has dignity and serenity, characteristics which have enabled her to withstand those who have tried to undermine the pioneering work undertaken by the team at Vrije Universiteit of Amsterdam. Not only the media but all too often other clinicians have been reluctant to accept the value of the Dutch approach to medical intervention during puberty, the former looking for a sensational headline and the latter fearing that their own long-held positions on the developing brain would be undermined.

Such hostility is almost inevitable when one works in a controversial field about which there is more general ignorance than professional knowledge. A quote of Charles Darwin comes to mind in considering the oppositional stance of Peggy's detractors: "Ignorance more frequently begets confidence than does knowledge."

Those who have criticized her work ignore a central tenet of the philosophy of science, which is that any scientific hypothesis or theory must have the characteristic of refutability by empirical experiment and observation. It must be possible to test the theory, empirically, to demonstrate whether or not it is false.

Fortunately, Peggy espouses knowledge, rather than the confidence that derives from ignorance, so she has actively taken up the challenge of testing the hypotheses. In doing so, and in communicating her findings to others, she has deployed her professional integrity, and her natural charm, as well as her other major weapon: her powerful intellect and its application to scientific methodology in the collection and interpretation of data.

Her willingness to give some credibility to the points raised by opponents, to put these to the test in her clinical observations, and to assemble the resulting data would, she hoped, eventually overcome ignorance and ill-founded beliefs. Certainly, Peggy has generated impressive data that are hard to dismiss. *Evidence* has been an effective weapon in her arguments against her detractors. Lack of evidence has been a notable weakness in theirs.

A growing number of practitioners in many countries now recognize the immediate uplift in mental health, and the ongoing benefits for adult life experiences, in those—carefully screened gender-variant individuals—who have undergone early suspension of puberty. As the recent WPATH Standards of Care (p. 20) acknowledge, although this intervention is not a neutral act, and there may be a preference among some clinicians to do nothing—*in dubio abstine*—the Standards also point out that in these circumstances, doing nothing is not a neutral act either. And doing no harm—*primum non nocere*—may *not* be achieved by allowing unwanted secondary sex characteristics to develop. Self-harm and suicidality are features of the untreated adolescent; they often disengage from social life and education. They continue into adult life with the mental scars, and permanent physical stigmata of the "wrong" sex, which are, if reversible at all, only partially so, and involve other health risks and considerable costs. This avoidable harm must be set against the unproven possibility postulated by those who disagree with pubertal intervention that phenotypic hormones will influence the brain to develop in the "correct" direction.

The rights of a child to a degree of autonomy should also be recognized; they have a right to say what is, and what is not, the "correct" direction for them. As with all gender dissonance, experienced at any age, it is only the person concerned who can tell clinicians how they feel and who they are. More studies are now available that show significant brain differences in transgender people, but these are not diagnostic, nor are they likely to be universal in the transgender population. Listening to children, in the broadest sense, not just to their actual words but observing their behavior too is therefore the best and the only true guide. Different nations have their own approach to legal protection and rights of minors, but the United Nations Convention on the Rights of the Child (1989) provides a benchmark for all. It states that children have rights to "Self-determination, dignity, respect, non-interference and to make informed personal decisions."

The ethical stance of Peggy and her colleagues ensures that these values are embedded in the care provided for their young patients.

Peggy passes on to us an important legacy. She is widely published in all relevant, prestigious, peer-reviewed journals and several books. She has made hugely valuable contributions to the development of the guidelines of the ESPE/LWPES (the European and American Societies for Pediatric Endocrinology) for diagnosis and treatment of DSDs; the World Professional Association for Transgender Health's recent *Standards of Care for the Health of Transsexual, Transgender, and Gender Nonconforming People*; and the Endocrine Society's Clinical guidelines: *Endocrine Treatment of Transsexual Persons*. She is currently the chair of the American Psychiatric Organization' s DSM-V Subworkgroup on Gender Dysphoria. She has thus made her profound knowledge and compassion available to wider circles of professionals.

Among Peggy's body of work, her contribution to the well-being of gender-variant youngsters stands out as arguably her greatest achievement. Peggy has spoken from the podium in many academic settings, including in London, in 2005, where she and Henriëtte Delemarre-van de Waal presented their findings to a small international symposium of clinicians covering: pediatric endocrinology, psychiatry, psychology, bioethics, and reproduction. These clinicians from Europe, the United States, and Australia were inspired to follow the Dutch lead and to spread the word to others. Even those who were initially skeptical are slowly capitulating.

Peggy's major contribution to medicine and to humanity is the fundamental principle that gender identity integrity is a human right and that enabling it in adolescents creates whole adults and saves lives. Intervention during puberty to alleviate the suffering of such young people has been the gift of Peggy and her team to the world.

It is a legacy to be proud of.

Louis Gooren and Jos Megens

Building a Center for Gender Dysphoria Research and Transgender Health Care: The Road from Wishful Thinking to Realization

The VU University Medical Center (VUmc) in Amsterdam, with its progressive Christian tradition, has a remarkable history of dealing with issues at the margins of society. Euthanasia, surrogacy, and, last but not least, transgender health care were controversial topics dealt with on academic grounds at VUmc. With Peggy Cohen-Kettenis' coming in 2002, again new ground was broken. She set about treating adolescents with severe gender dysphoria. Over time, much evidence has been accumulated that gender identity disorders are based on endogenous factors and may present themselves as early as 3 years. The work of diagnosing gender identity disorders in children and adolescents and developing treatment options for adolescents was a long road, fraught with obstacles. With the support of an established gender team and a socially open-minded university, her research on and treatment of gender-dysphoric children and adolescents became increasingly respected. To date, many clinics and countries around the world have adopted the protocols of the "Amsterdam Center of Expertise on Gender Dysphoria."

In the 1980s, the Dutch pioneers of transgender health care recognized the importance of multidisciplinary cooperation for transgender health care. Over time this cooperation gradually developed into a well-coordinated interdisciplinary team making informed decisions.

To succeed in building up a true "gender team," it is essential to agree on a framework of common objectives. The many issues include the following: team premises, team composition, organizational support, team meetings, communication skills, and clear goals and objectives. Generally speaking, the obstacles and resistance to multidisciplinary collaboration reflect the diversity of cultures across various disciplines. Surgeons are professionally socialized differently than internal medicine specialists, and mental health-care providers communicate differently from somatically oriented doctors. Additionally, it is unique that medical specialists concerned with sex reassignment do not make a separate diagnosis but are required to trust the diagnosis and indication of mental health-care providers. The necessity and the advantages of a team brought together to serve transgender patients will hardly be questioned, but the task of realizing a true "gender team" is something different and challenging.

As a matter of fact, many psychological skills are necessary to build a team with a sense of common purpose. In Amsterdam, professionals from as many as 13 different disciplinary backgrounds share a common endeavor and perform different roles based on different knowledge bases and objectives. Nobody has managed to reconcile so many different interests better than Peggy Cohen-Kettenis. It is clear that gender teams need psychologists not only for patient care but also to appease claims and demands from singular disciplines which may attempt to contradict the all-encompassing, integrated approach.

Some possible barriers to sufficient cooperation among professionals in the medical context are specialization and exclusivity, effusive use of jargon, administrative barriers, unwillingness to disseminate knowledge, professional competition, and the (battle)fields along the boundaries between disciplines. It is important to address these common pitfalls of multidisciplinary teams on a regular basis rather than ignore these possible adversities.

Moreover, it is essential for gender teams to agree on the fact that the entire medical intervention is dedicated to two major goals: diminishing gender dysphoria and social reintegration in accordance with the experienced gender identity. This means that medical disciplines need to accept that the diagnosis of gender dysphoria and the indication for treatment are under the primary responsibility of mental health professionals. Mutual dependence of mental health-care providers and physical health-care providers is not a pitfall, but an opportunity for gender teams to improve competence. The acceptance of psychological diagnostic hegemony, as well as end points beyond the borders of physical treatment, may alter our mind-set in a way to give hope for the future that gender dysphoria will be depathologized.

In a way, gender teams can be considered an experimental design for future innovative multidisciplinary partnership models. Gender teams not only deal with shared decision-making among various medical professionals and psychologists but also deal with the huge societal impact of treating individuals beyond traditional dichotomous patterns of gender assignment. Transgender persons often do not consider themselves to be patients and may not wish to be defined in the role of a patient. Professionals need to accept the self-concept of the individual and the right to be different from the professionals' expectations. To date men and women in most developed countries are legally entitled to live and behave according to their own experienced gender identity. However, these rights might sometimes conflict with professional standards of care and experience. Competent gender teams will need to grapple with the tension between sticking to the professional standards of care while at the same time respecting the individual patients' right of self-determination.

Future gender teams will have a different set of requirements. On the one hand, there are many with scientific interests in unraveling the conditions and effects of the gender dysphoria phenomenon, and the professional community is asking for carefully considered interventions with awareness of possible comorbidity. On the other hand, eager and restless patients are desperately asking for help in the context of steadily growing societal pressure to enable persons with gender identity incongruence to live according their experienced gender identity.

Peggy Cohen-Kettenis has set indelible landmarks not only for the treatment of gender-dysphoric children and adolescents but also for the management of future gender teams: She is not only a profoundly committed team worker but also an enthusiastic advocate of evidence-based principles and a strong supporter of the human right to live in accordance with one's experienced gender identity. If a gender team respects these strong characteristics, there is no doubt that it will be successful, both for the benefit of future transgender persons and for the professional satisfaction of health-care providers.

It has been a privilege to head the Amsterdam Gender team arm in arm with Peggy over the years. These years are unforgettable. Peggy's contagious enthusiasm and tenacious adherence to the principles of teamwork and evidence-based treatment have truly made a lasting impression on me and others. With eagerness, we will continue the way Peggy has sketched out, as a team.

Mick van Trotsenburg

This Book

The aim of this book is to provide a state-of-the-art review on the care and current scientific knowledge regarding gender dysphoria (GD) and disorders of sex development (DSD). Its purpose is to inform the reader about the *history, the present situation, and the most recent developments and new perspectives* in research and clinical management of children, adolescents, *and* adults with GD and DSD. This book aims to be a unique and comprehensive handbook through the contributions from a selection of the leading scientists and established clinicians in the field of GD and DSD, focusing on the following: the etiologic and developmental trajectories of both phenomena regarding gender identity development, psychiatric comorbidity, classification dilemmas, ethical dilemmas in treatment, influences of societal stigmatization, discussing the medical and psychological implications and outcomes of treatment, and providing treatment guidelines for individuals with GD *and* DSD, among children, adolescents, *and* adults. By presenting this overview of the past, the present situation, and challenges for the future, the book aims to inform the reader about the needs for further research and to stimulate the development and improvement of clinical care in individuals with GD and DSD.

The first three chapters concern the etiology of gender dysphoria and factors that contribute to gender identity development. Chapter 1 by Julie Bakker focuses on the role of sex hormones on the sexual differentiation of the brain and reviews the large body of literature on relevant animal studies. Chapter 2, written by Daniël Klink and Martin den Heijer, deals with the current knowledge of genetic factors involved in gender identity development and gender dysphoria. They present their ideas for future genetic studies in the field of gender dysphoria. Chapter 3 by Annelou de Vries, Baudewijntje Kreukels, Thomas Steensma, and Jenifer McGuire presents an overview of psychological, social, and biological factors that have been studied for their role in gender identity development. They seek to integrate these factors in a biopsychosocial model but have to conclude that this integration still needs to be supported by research findings.

The second part presents three chapters on disorders of sex development. Chapter 4 is authored by Faisal Ahmed. He considers the early care of infants with a suspected disorder of sex development and highlights the problems encountered in this early phase of diagnosis and treatment. Chapter 5 by David Sandberg and Tom Mazur presents a noncategorical approach to the psychosocial care of persons with DSD and their families. They propose an integrated team care model that is patient and family centered. Chapter 6, written by Birgit Köhler, Martina Jürgensen, Eva Kleinemeier, and Ute Thyen, focuses on psychosexual development of people with DSD and presents the work of the German clinical evaluation study of people with DSD.

The last part of the book is devoted to gender dysphoria. Jack Drescher reviews the history of psychiatric and medical theorizing about transsexualism and transgender presentations in Chap. 7. In addition, he presents the evolution of classification and nomenclature of gender identity diagnoses in the International Statistical Classification of Disease (ICD) of the World Health Organization and the Diagnostic and Statistical Manual (DSM) of the American Psychiatric Association.

The following four chapters deal with gender dysphoria in childhood and adolescence. Chapter 8 by Domenico Di Ceglie starts with the care for gender-dysphoric children. He illustrates the guidance of children with gender dysphoria by the work of the Gender Identity Development Service in London. In Chap. 9, Ken Zucker, Hayley Wood, and Doug VanderLaan present an overview of empirical data on the extent to which children and adolescents with gender dysphoria show other types of psychopathology or behavior problems. They consider models for psychopathology in children and adolescents with gender dysphoria. Chapter 10 is written by the first pediatric endocrinologist who engaged in puberty suppression in adolescents with gender dysphoria, Henriëtte Delemarre-van de Waal. She explains how this protocol was developed and summarizes the first research findings. Simona Giordano analyzes ethical and legal concerns around medical treatment for children and adolescents with gender dysphoria in Chap. 11.

The final section of the book offers six chapters on adults with gender dysphoria. It starts with Chap. 12 by Griet De Cuypere and Luk Gijs who explore the history of the care of adults with gender dysphoria by the evolution in the various versions of the Standards of Care of the World Professional Association of Transgender Health. Theoretical models to explain psychiatric comorbidity in adults with gender identity problems are discussed in Chap. 13 by Luk Gijs, Ellis van der Putten-Bierman, and Griet De Cuypere. The book continues with the contribution of Louis Gooren and Henk Asscheman, Chap. 14, on endocrinological interventions in adults with gender dysphoria. They also focus on side effects and hormone-dependent cancers in people treated with cross-sex hormones. Chapter 15 considers sex reassignment surgery and highlights the contemporary techniques used. This chapter is written by Stan Monstrey, Marlon Buncamper, Mark Bram Bouman, and Piet Hoebeke. The impact of stigma on transgender identity development and mental health is the topic of Chap. 16 by Walter Bockting. The last chapter of the book, Chap. 17, by Friedemann Pfäfflin, reflects on the history of the term "identity" in general and the terms "sexual and/or gender identity" in particular, as well as political implications of their use in the context of psychiatric diagnoses.

Terminology

The terminology in the field of Gender Dysphoria and Disorders of Sex Development is rapidly changing and tends to vary among the different disciplines. Variations in terminology used by the different authors in this book were therefore inevitable. To ensure that the quality of the contributions by the various authors would not be affected, we therefore chose to keep the terminology in the style as presented by each author.

Amsterdam, The Netherlands

Baudewijntje P.C. Kreukels
Thomas D. Steensma
Annelou L.C. de Vries

Acknowledgements

We would like to express our gratitude to all the individuals who have helped us to publish this book for the occasion of the retirement of Peggy Cohen-Kettenis. First we would like to thank the authors, all of our colleagues from the Center of Expertise on Gender Dysphoria, and all of those people outside our team for keeping this a secret from Peggy. We hope that it will be a real surprise for her on the day of the symposium for her retirement in June 2013.

How an Informal Conversation to the Train Station Resulted in a Lot of Work

The idea for this book started during a shared walk to the train station of *Hanneke Kempes* and *Luk Gijs.* Sometime in February 2012 they were exchanging ideas for Peggy's good-bye. Luk mentioned that it would be nice to present her a book. Hanneke called Baudewijntje the next day to share this idea. She liked it immediately, although she guessed that it would be a very time-consuming project and realized that it had to be kept a secret for Peggy. Baudewijntje invited Annelou, who was keen from the start to join her in this endeavor. Soon afterwards Thomas offered his help, although he also had to finish *his other book.* Hanneke proposed to assist us in all administrative tasks.

We would like to express an extra thank you to a few people for helping us in the process to get this book published. The initial idea was to collect a few chapters and have them printed. At Oslo airport, with Peggy around the corner, *Walter Bockting* expanded the idea by proposing to get the book published by an official publisher or to present it as a special issue of a journal. Soon after a conversation with *Louis Gooren,* sometime in April, we turned to *Ken Zucker* and presented our ideas; he immediately introduced us to *Marta Meana* who was the series editor for a Springer book series entitled "Focus on Sexuality Research." She was interested and helped us to put together a proposal for Springer. We would like to thank her for her help in this crucial phase. The proposal was then sent to *Carol Bischoff* at Springer, who approved our plans. We were delighted with her interest in the book proposal and we received the contract shortly afterwards. We would like to thank Carol and Marta for their confidence in this project and their willingness to publish this book. It was a pleasure to work with you. *Sylvana Ruggirello* was the editorial assistant at Springer who handled the contract; she always replied promptly to our questions and was efficient and quick throughout the process.

At the end of June, we signed the contract and started inviting authors in early July 2012. Because we planned to present a mockup of the book in June 2013, the final manuscript had to be sent to Marta Meana the 1st of February 2013. Our time frame was thus very tight. Nevertheless, we soon found out that getting authors to contribute was not that difficult when we used the magic sentence: "*It is for Peggy Cohen-Kettenis.*" Everybody immediately expressed their interest, coupled with a willingness to work overtime to help us in this endeavor to reach our deadline. We asked all authors to send us their first draft in October 2012. We were delighted (and relieved) that we reached our deadline with all the contributions to this book for Peggy. *Julie Bakker, Daniel Klink, Martin Den Heijer, Jenifer McGuire, Faisal Ahmed, David Sandberg, Tom Mazur, Birgit Köhler, Martina Jürgensen, Eva Kleinemeier, Ute Thyen, Jack Drescher, Domenico Di Ceglie, Kenneth Zucker, Hayley Wood, Doug VanderLaan, Henriëtte Delemarre-van de Waal, Simona Giordano, Griet De Cuypere, Luk Gijs, Ellis van der Putten-Bierman, Louis Gooren, Henk Asscheman, Stan Monstrey, Marlon Buncamper, Mark Bram Bouman, Piet Hoebeke, Walter Bockting, and Friedemann Pfäfflin*, thank you very, very much for your quick work, your well-written chapters, and your responses to our numerous emails. It was always a real pleasure to read all of your chapters, we have enjoyed working with you, and you have made this book a valuable contribution to the field of Gender Dysphoria (GD) and Disorders of Sex Development (DSD).

Walter Everaerd, Hanna Swaab, Louis Gooren, Jos Megens, and Mick van Trotsenburg were so kind to give us their personal descriptions of their view on Peggy's career; thank you for these nice overviews that build the preface of this book.

We were extremely happy to have *Jenifer McGuire* working with us and being our associate editor. She has helped us enormously with her ideas, by editing the chapters of the non-English writers and as a coauthor for our own chapter. She always worked through the manuscripts quickly and joined us frequently when we met to discuss the progress.

Guy T'Sjoen helped us review some of the medical chapters really quickly; thank you. Daniel Klink stepped in immediately when one of the authors had to withdraw his contribution and together with Martin Den Heijer he wrote one of the longest chapters in this book in no time. We thank *the International Journal of Transgenderism*, *the World Professional Association for Transgender Health,* and *Friedemann Pfäfflin* for their financial support to reprint the last chapter. And we thank *Walter Bockting* for assuring that this arrangement could be made.

We especially would like to thank *Arnoud*, *Babet,* and *Melle*, *Christie*, *Lodeis,* and *Caelis*, and *Cathrine* and *Anna* for supporting us, being flexible at home, and

keeping spirits up, although it was sometimes hard to combine the extra work with other extra work and family matters.

Last but not least, we would like to thank Peggy for being the inspiration of this book! During the years that we have worked under your scientific supervision, we have learned innumerable lessons about this unique and special field of GD and DSD. We will always carry your wisdom with us while we hope to build further on what you have started.

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Part I
Developmental Principles

Chapter 1
Sex Differentiation: Organizing Effects of Sex Hormones

Julie Bakker

Abstract Men and women differ, not only in their anatomy but also in their behavior. Research using animal models has convincingly shown that sex differences in the brain and behavior are induced by sex hormones during a specific, hormone-sensitive period during early development. Thus, a male-typical brain is organized under the influence of testosterone, mostly acting during fetal development, whereas a female-typical brain is organized under the influence of estradiol, mostly acting after birth, during a specific prepubertal period. Sex differences in behavior reflect sex differences in the brain, mostly in the hypothalamus and the olfactory system, the latter being important in mate selection. There is also evidence, albeit clinical, for a role of testosterone in the sexual differentiation of the human brain, in particular in inducing male gender role behavior and heterosexual orientation. However, whether estradiol is involved in the development of a female brain in humans still needs to be elucidated.

1.1 Introduction

For decennia, the origin of sex differences in the brain and behavior has been the subject of heated debate. In particular, whether sex differences observed in adulthood result from specific biological processes occurring during early development ("nature") or from the (social) environment ("nurture"). There is increasing evidence, however, that the organization of the brain is affected by circulating sex

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hormones and the expression of specific genes during early development and thus that sex differences in brain structure and organization are already present as early as birth. The biological bases of sex differences in brain and behavior are becoming better known, but many questions remain about how sex hormones induce such different patterns of neural and behavioral differentiation in men and women. This chapter will provide a short overview of our current knowledge of how the sexual differentiation of the brain proceeds under the influence of organizing actions of sex hormones. Many of our ideas about the sexual differentiation of the human brain are derived from research on animal models, in particular in rodent species, such as mice and rats. Therefore, this chapter will mostly review results obtained in animal models, but a short overview will also be provided of the sexual differentiation of the human brain, particularly in relationship to sexual orientation and gender identity.

1.2 Classical Theory of Brain and Behavioral Sexual Differentiation

In mammals, including humans, the developing organism has the potential to become either male or female. The first step in the process of sex determination is the establishment of the genetic sex at conception. Each cell nucleus contains a species-specific number of paired autosomes and two sex chromosomes. For example, humans have 22 pairs of autosomes and 1 pair of sex chromosomes (the X and Y). Autosomes are numbered roughly in relation to their sizes, i.e., chromosome 1 has approximately 2,800 genes, whereas chromosome 22 has approximately 750 genes. The sex chromosomes will determine the sex of the fetus: females have two X chromosomes, whereas males have one X and Y chromosome. The latter contains a specific gene, the *Sry* gene, which will induce the formation of testes from the undifferentiated gonads in males (Koopman, Munsterberg, Capel, Vivian, & Lovell-Badge, 1990). The Leydig cells in the testes will produce testosterone which will promote the development of the Wolffian ducts into the internal male genital structures such as the epididymis, the vas deferens, and the seminal vesicles, whereas anti-Müllerian hormone secreted by the Sertoli cells in the testes causes regression of the female-typical Müllerian ducts. The penis and scrotum develop under the influence of dihydrotestosterone which is formed from testosterone by the enzyme, 5α-reductase (see Fig. 1.1). In typical female differentiation, i.e., in the absence of the Y chromosome and consequently the *Sry* gene, the undifferentiated gonads will develop into ovaries. The Müllerian ducts develop without any apparent hormonal input into the uterus, fallopian tubes, and the distal portion of the vagina, whereas the Wolffian ducts regress and disappear in the absence of androgenic stimulation (see Fig. 1.1).

Phoenix, Goy, Gerall, and Young (1959) were the first to provide important evidence that the capacity to display sex-specific behaviors in adulthood

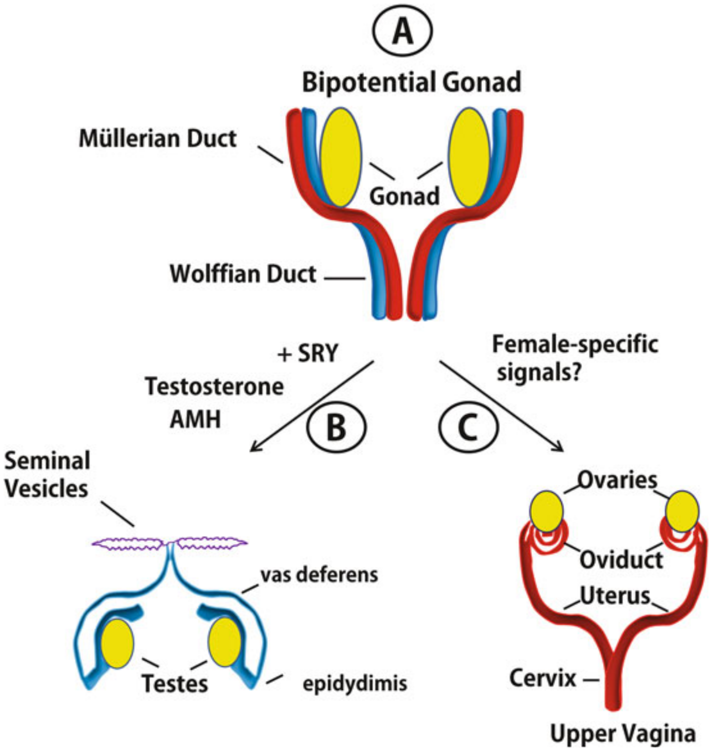

Fig. 1.1 The development of the genital structures. The key event is the presence of the SRY gene on the Y chromosome, since it triggers the development of testes, which will in turn secrete testosterone and anti-Müllerian hormone (AMH), leading to the development of male-typical genital structures

(and by inference, the sexual differentiation of the brain) follows the same pattern as that of the genitals. They reported that female guinea pigs which were treated with testosterone during prenatal development showed elevated levels of male-typical mounting behavior, together with reduced levels of female-typical lordosis behavior when tested in adulthood (Phoenix et al., 1959). Lordosis behavior is a typical mating posture observed in female rodents characterized by an immobile posture with an arched back which enables the male to intromit the female and thereby to fertilize her (see Fig. 1.2). These results thus showed for the first time that testosterone had organizational effects on the brain, i.e., it masculinizes and defeminizes aspects of sexual behavior, such as increasing male-typical sexual behavior, such as mounting a female, and decreasing female-typical sexual behavior such as the display of the lordosis reflex when mounted by a male. In addition to these organizational effects, it is important to note that gonadal hormones also have important activational effects on the display of sexual behavior. For instance, male sexual behavior is highly dependent on testosterone produced by the Leydig cells of the testes. In all mammalian species studied, the display of mating behavior in adult

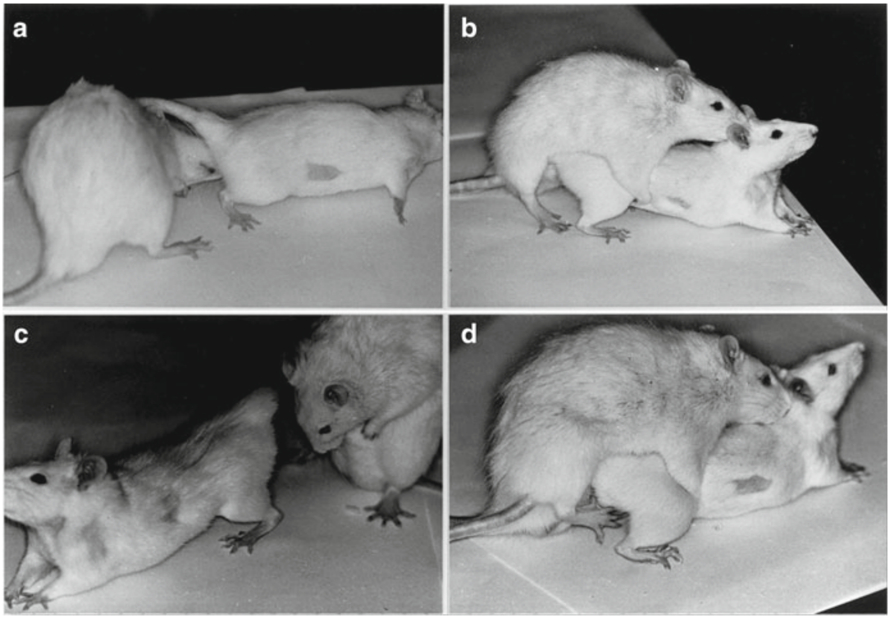

Fig. 1.2 Sexual behavior in rats. A male first investigates the perineal region of the female (**a**). If the female is in estrus, the male mounts her with his forepaws clasped against her hindquarters. This tactile stimulation causes her to display the lordosis posture, that is, arching her back and deflecting her tail (**b**). After a few seconds, the male dismounts the female and grooms himself (**c**). After several mounts and intromissions, the male ejaculates (**d**)

males is stimulated by testosterone. The increase in testosterone production at puberty underlies the increase in sexual activity in maturing males, and if the source of testosterone, the testes, is removed surgically, sexual activity typically declines. Likewise, in most female species (with the exception of some primate species and humans), sexual behavior coincides with ovulation and thus with high levels of the ovarian hormones, estradiol and progesterone. When the ovaries are removed, the female will no longer show any sexual behavior. By contrast, in ovariectomized females, sexual behavior can be induced by appropriately timed injections of estradiol and progesterone, thereby mimicking the estrous cycle. Sexual behavior will thus be elicited when the female is in a state of estrus (and thus fertile).

Additional support for the organizing role of testosterone in the development of male sexual behavior and, by inference, the brain came from subsequent studies by Feder and Whalen (1964) and many others (reviewed in Baum, 1979). These studies showed that male rats that were castrated within 1 day after birth displayed reduced levels of male-typical mounting behaviors when supplemented with testosterone in adulthood. Furthermore, when treated with the ovarian hormones estradiol and progesterone in adulthood, these neonatally castrated males displayed female-typical lordosis behavior when mounted by another male. However, when male rats were castrated as late as day 10 after birth, they showed typical levels of male sexual behavior upon treatment with testosterone and no female sexual behavior upon treatment with estradiol and progesterone, in adulthood. This indicates that the organizing actions of testosterone on the brain proceed during a restricted developmental period. Conversely, female rats treated with testosterone within the first week after birth (but not at later postnatal ages) showed increased mounting behavior when paired with another female and less lordosis behavior when paired with a male, when tested in adulthood for their sexual behavior. The observation that neonatally castrated male rats were capable of showing female-typical lordosis behavior led to the conclusion that the development of the female brain and thus the capacity to show female-typical sexual behaviors proceeds in the absence of any hormonal secretion, i.e., by default. Consistent with this view is the observation that the rodent ovary does not secrete any significant amounts of estradiol before postnatal day 7 (Lamprecht, Kohen, Ausher, Zor, & Lindner, 1976), whereas the testes start to produce testosterone about 1 week before birth in rodents.

To summarize, the ability to show the complete pattern of male sexual behavior in adulthood is the result of a process called the sexual differentiation of the brain which occurs during a restricted developmental period under the influence of testosterone. The duration and timing of this "critical period" is species-specific. For instance, in rats, the critical period in which the animal is maximally susceptible to the organizing actions of testosterone on the brain extends approximately from day 14 of prenatal life (gestation lasts 21–22 days in rats) to day 10 of postnatal life. Prenatally the developing testes start to secrete testosterone at day 14, and surges in testosterone release have been detected on prenatal days 18 and 19. Postnatally, there is a surge in testosterone in males directly after birth followed by a sharp decline approximately 6 h later. Testosterone levels remain higher in males than in females until day 10 after birth, after which they drop and remain low until the age of puberty.

In addition to sex-specific coital behaviors, motivational aspects of sexual behavior, such as seeking out a mating partner, known as "sexual partner preference" or "sexual orientation," are also sexually differentiated by the presence of testosterone during early development (reviewed in Bakker, 2010). Motivational aspects of sexual behavior are usually determined by providing a choice between a sexually active male and an estrous female or between an anestrous female and an estrous female in a maze or three compartment box (see Fig. 1.3). In the majority of these studies, the time spent in the proximity of each stimulus animal is used as a measure of preference. Overall, gonadally intact male rats prefer estrous females over males and this preference occurs even without prior sexual experience. Conversely, females in behavioral estrus prefer males over females. Thus, when female rats were treated with testosterone shortly after birth and then tested for their partner preference in adulthood, they preferred to approach the female instead of the male. Likewise, male rats castrated at birth and then tested in adulthood for partner preference upon receiving testosterone, spent less time near the female than male rats that were left gonadally intact. These studies thus imply that testosterone organizes a male-typical partner preference, i.e., a preference to seek out an estrous female during early development, as was also shown for the ability to display typical male coital behaviors.

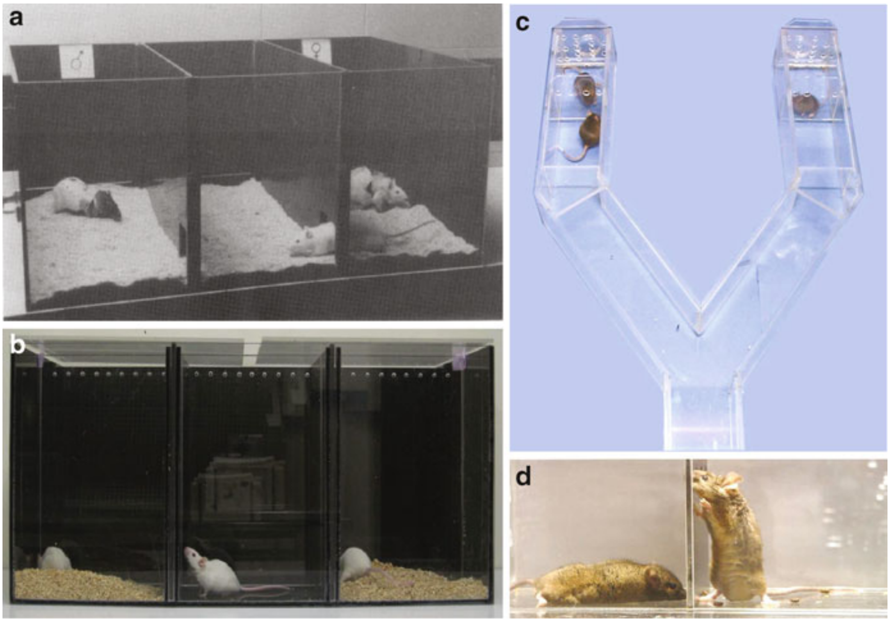

Fig. 1.3 Examples of behavioral devices that can be used for measuring partner or odor preferences in rats and mice. (**a**) For measuring partner preference in rats, a sexually active male and a female brought into behavioral estrus are placed in the lateral compartments and the experimental subject in the middle compartment. The time spent by the experimental animal visiting the two compartments is recorded. (**b**) For measuring odor preferences in mice, a sexually active male and a female brought into behavioral estrus are placed in the lateral compartments and the experimental subject in the middle compartment. The time spent by the experimental animal sniffing the two compartments is recorded. (**c**) Alternatively, a Y maze can be used for measuring odor preferences in mice. The stimulus animals are placed in the goal boxes at the end of each arm. To prevent the experimental animal from hearing the stimulus animals (since rodents use ultrasonic vocalizations for communication), the stimulus animals can be anesthetized (**d**)

1.3 The Aromatization Hypothesis

A remarkable finding has been that the conversion of testosterone to estradiol in brain cells by the aromatase enzyme presents a crucial step in the sexual differentiation of the male rodent brain (Naftolin et al., 1975). At first glance this seems to be counterintuitive since estradiol has always been considered a female-typical hormone. Furthermore, it has been generally thought that estradiol was only synthesized and secreted by the ovaries, but aromatase, the critical estradiol-synthesizing enzyme, is also present in the brain. There is strong evidence that estradiol is actually responsible for many of the organizing effects of testosterone on the developing brain (reviewed in Bakker, 2010). To give just one example out of many available, when newborn male rats were treated with the aromatase inhibitor, 1,4,6-androstatriene-3,17-dione (ATD), thereby pharmacologically blocking the conversion of testosterone to estradiol, they showed less male-typical mounting behavior and more female-typical lordosis behavior in adulthood. In fact, their behavioral phenotype was strikingly similar to what is observed when male rats were castrated at birth. The important role of brain aromatase in the development of the male brain is also known as the *aromatization hypothesis*.

It should be noted that the predominant role of estradiol in organizing male sexual behavior may be limited to the rat. Studies using genetically engineered mice suggest a role for testosterone itself in organizing male sexual behavior since male mice carrying a mutation in the aromatase gene (aromatase knockout or ArKO) showed full-blown male mating behavior provided that they were supplemented with estradiol in adulthood since they cannot synthesize estradiol themselves (Bakker, Honda, Harada, & Balthazart, 2004). These findings suggest that these behaviors are not organized by estradiol during early development. However, these studies showed that testosterone needs to be aromatized to estradiol in order to activate the behavior in adulthood. Further support for the predominant role of testosterone in organizing male sexual behavior in the male mouse is found in studies using male mice in which the androgen receptor was invalidated. Such males showed major deficits in the expression of male sexual behavior (Sato et al., 2004).

Numerous studies on rats and mice suggest that many of the organizational actions of testosterone on the differentiation of male-typical profiles of partner preference also depend on the aromatization of testosterone to estradiol in the male brain (reviewed in Bakker, 2010). An early series of studies on rats showed that administration of the aromatase inhibitor ATD to newborn male rats duplicated the long-lasting effects of neonatal castration on partner preference. When tested in adulthood, males treated neonatally with ATD preferred to approach the stimulus male (and showed lordosis when mounted by the stimulus male) instead of an estrous female.

To date, few studies have investigated the role of testosterone versus estradiol in the differentiation of male-typical partner preference in mice. Most of these studies have focused on the role of estradiol. In one such study, male mice with an invalidated estradiol receptor α (ERα) showed no preference for an estrous female over a stimulus male with both stimulus animals being placed in the opposite ends of a runway, whereas control males (named wild type) preferred the estrous female (Wersinger & Rissman, 2000). However, it is not clear from this study whether the disruption of estradiol signaling reflected an organizational or activational role of estradiol on partner preference. Unfortunately, results obtained from the ArKO mouse model (with a mutation in the aromatase gene and thus deprived of estradiol) failed to resolve this issue (Bakker, Honda, Harada, & Balthazart, 2002, 2004). It was found that wild-type males preferred to approach odors emitted from an estrous female as opposed to a gonadally intact male, whereas ArKO males showed no preference for one stimulus over the other. However, this difference was not reversed by adult treatment with estradiol, which suggests a possible contribution of perinatal estradiol to male-typical odor preferences, but ArKO males never showed a female-typical preference for male odors. A more recent study (Bodo & Rissman, 2007) actually suggests that testosterone acting through the androgen receptor might be important for partner preferences in mice. Female mice which have been treated with dihydrotestosterone on the day of birth showed a male-typical preference, i.e., they preferred the odors from estrous females over those from intact males. Control females preferred male odors. These results thus show that testosterone acting through the androgen receptor masculinizes partner preferences in mice.

It is generally assumed that any estradiol produced by the gonads (either testes or ovaries) does not play a role in the sexual differentiation of the brain because its passage into the brain is prevented by the presence of high concentrations of a plasma glycoprotein, alpha-fetoprotein. This protein is produced in high quantities by the fetal liver and binds estradiol with high affinity in rats and mice (Raynaud, 1973). Presumably, alpha-fetoprotein reduces the free, biologically active fraction of estradiol to a concentration which is too low to enter the brain. Serum levels of estradiol are quite high during gestation, with the mother's ovaries as the major source. In both male and female rats, serum levels of estradiol decrease between the final fetal stage (day 21) and 24 h after birth, further supporting that any estradiol circulating before birth is of maternal source. By contrast, there is a small surge in estradiol in the hypothalamus of male rats just after birth (between 0 and 1 h after delivery), followed by a sharp decrease. This hypothalamic estradiol surge is completely absent in female rats. The increase in hypothalamic estradiol in male rats actually coincides with the surge in testosterone at birth, suggesting that it results from a conversion of testosterone by the aromatase enzyme locally in the brain. Indeed, the activity of the aromatase enzyme measured on the day of birth is much higher in the male than in the female brain (Bakker, Baillien, et al., 2004). In female rodents, serum levels of estradiol start to increase again after postnatal day 5, with a peak level around postnatal day 15, and then estradiol levels drop again by postnatal day 25, before increasing again at puberty. The source of this estradiol is most likely the ovaries, which—in contrast to the testes—are quiescent during prenatal development. In vitro studies have shown that the rodent ovary does not secrete significant amounts of estradiol before postnatal day 6–7 (Lamprecht et al., 1976). The observations that the ovaries are quiescent during perinatal development and that any estradiol produced by the mother is bound to alpha-fetoprotein further support the assumption that the neural mechanisms which control later female-typical sexual behavior normally develop perinatally in females "by default," i.e., without the need for any hormonal stimulation. Indeed, it was recently observed using mice with a targeted mutation of the *Afp* gene and thus deficient in alpha-fetoprotein (AFP-KO) that alpha-fetoprotein protects the fetal (female and male) mouse brain from being defeminized and masculinized by maternal estradiol (Bakker et al., 2006). Thus, AFP-KO female mice displayed no

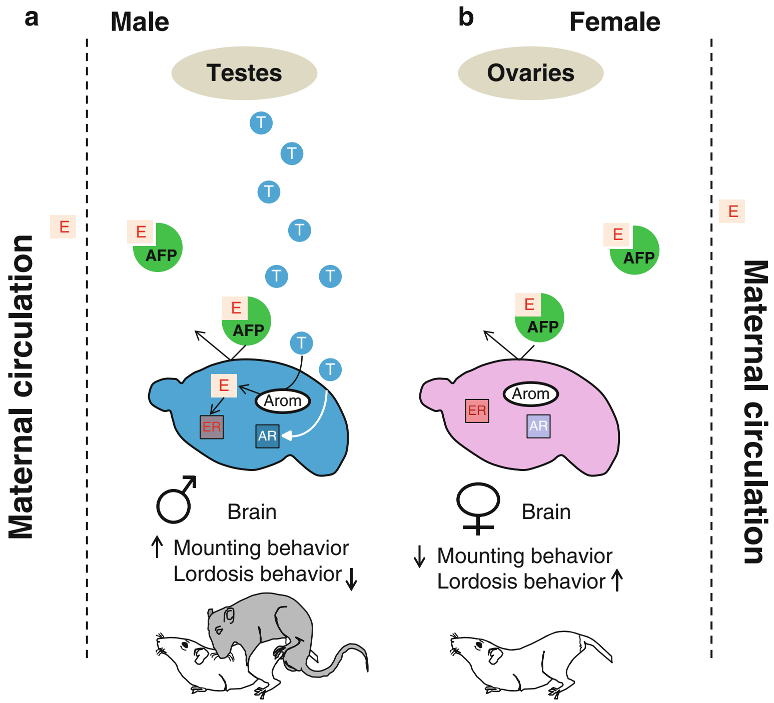

Fig. 1.4 Schematic overview of how sex hormones induce a male- or female-typical differentiation of the brain and behavior. In the male, testosterone (T) produced by the developing testes reaches the brain where it will be converted to estradiol (E) by the enzyme aromatase (Arom). Estradiol will then bind to specific estradiol receptors (ER) leading to a cascade of gene expression ultimately leading to a male-typical brain, i.e., an increase in mounting behavior and a decrease in lordosis behavior in adulthood. T can also affect directly the development of the brain by binding to androgen receptors (AR). In the female, any estradiol coming from the mother is bound to alpha-fetoprotein (AFP) and thus prevented from entering the brain leading to a female-typical brain, i.e., a decrease in mounting behavior and an increase in lordosis behavior in adulthood

female sexual behavior after adult ovariectomy and treatment with estradiol and progesterone. However, when estradiol synthesis was blocked during embryonic development by maternal administration of the aromatase inhibitor, ATD, the capacity of female offspring to show female sexual behavior in adulthood was rescued. These data provide strong evidence that during fetal life, the main contribution of estradiol is to promote male-typical brain and behavioral sexual differentiation—an action that is blocked in female fetuses by the binding of any circulating estradiol by AFP (see Fig. 1.4).

1.4 The Role of Estradiol in the Feminization of the Brain

The possible importance of ovarian hormones in female-typical brain sexual differentiation was first suggested by some early behavioral studies in the 1960–1970s which showed that female rats ovariectomized on the day of birth showed less lordosis behavior following adult treatment with estradiol and progesterone than females that either kept their ovaries or were ovariectomized at birth and at the same time implanted with ovaries until postnatal day 60 (Gerall, Dunlap, & Hendricks, 1973). In addition, an in vitro study showed that estradiol promoted neurite outgrowth from fetal hypothalamic brain slices of both sexes, suggesting a role for estradiol in neural differentiation (Toran-Allerand, 1976). More recently, Dohler and coworkers showed in 1984 that neonatal treatment of female rats with tamoxifen, an estradiol receptor antagonist, decreased their later capacity to show lordosis behavior whereas concurrent neonatal administration of a low dose of estradiol prevented this effect. Finally, Baum and Tobet (1986) found that female ferrets treated prenatally with the aromatase inhibitor, ATD, and then treated in adulthood with a low or moderate dose of estradiol displayed reduced female sexual behavior when paired with a stimulus male.

These various behavioral results suggested that exposure to a low level of estradiol over a postnatal interval between birth and the age of puberty facilitated the later capacity to display female sexual behavior; however, they did not provide indisputable evidence that estradiol normally contributes to the development of female sexual behavior in female mammals. First, the effects of neonatal ovariectomy on the potential to show lordosis behavior later in life were only transient since any differences in lordosis behavior disappeared following repeated testing. Perhaps more importantly, in addition to its anti-estrogenic actions, tamoxifen can exert estrogen-like agonist actions in the brain. Therefore, the observed reduction in lordosis behavior induced by administering tamoxifen neonatally to female rats may actually have resulted from a partial defeminization of the brain by the estradiol-like actions of tamoxifen acting on neural estradiol receptors. Finally, prenatally ATD-treated female ferrets and control females displayed equivalent, that is, high, levels of female sexual behavior when tested after receiving a high dose of estradiol in adulthood, again indicating that ATD-treated females were capable of displaying normal female-typical receptive behavior. Thus, it had been difficult to provide conclusive evidence of a role for estrogens in the development of the female brain. As a result, the hypothesis languished since the mid-1980s due to the absence of a suitable animal model in which the possible contribution of estradiol to the development of the female brain could be rigorously assessed. The creation of the aromatase knockout (ArKO) mouse (Honda, Harada, Ito, Takagi, & Maeda, 1998) provided an opportunity to reopen work on this hypothesis. Since ArKO mice cannot produce estrogens themselves due to a targeted mutation in the aromatase (*Cyp19*) gene, but do have functional estradiol receptors, they can respond to exogenous estradiol at any time during their life span. This means that this model can be used to distinguish between organizational and activational effects of estradiol on brain and behavioral functions. Female ArKO mice, treated with estradiol and progesterone in adulthood, displayed less lordosis behavior when paired with a stimulus male and showed a reduced investigation of odors from male or female mice suggesting, once again, that estradiol normally contributes to the development of the neural mechanisms that control these female-typical behaviors. In contrast with earlier studies (Gerall et al., 1973), the reduction in lordosis behavior observed in ArKO females did not disappear with repeated testing, suggesting permanent effects of early estradiol deprivation on the later potential to show female sexual behavior.

1.5 Possible Differences in the Perinatal Timing of Estradiol's Action in Male Versus Female Brain

An obvious question raised by the proposition that estradiol plays an essential role in the development of female-typical behavior is how this hormone can induce both male-typical (i.e., defeminization and masculinization) and female-typical (i.e., feminization) neural differentiation? There are two possible answers to this question. First, quantitative sex differences in brain estradiol synthesis may be one mechanism by which a male, as opposed to a female, brain develops. Thus, in the genetic female, prenatal exposure of the brain to low "priming" concentrations of estradiol may elicit neural growth and differentiation in a female-specific manner. The source of estradiol is probably the brain itself since any estrogens in the circulation are not available to the female brain because they are bound to alphafetoprotein (Bakker et al., 2006; McEwen, Plapinger, Chaptal, Gerlach, & Wallach, 1975). The higher levels of circulating testosterone (Pointis, Latreille, & Cedard, 1980) and brain aromatase activity (Bakker, Baillien, et al., 2004; Beyer, Wozniak, & Hutchison, 1993; Hutchison, Beyer, Hutchison, & Wozniak, 1995) available perinatally in the male brain may produce higher local neural concentrations of estradiol in male rodents and thereby induce a male-typical profile of brain sexual differentiation. Indeed, estradiol levels were reportedly higher in the frontal cortex, hypothalamus, and preoptic area of male versus female rats when measured within 2 h after birth (Amateau, Alt, Stamps, & McCarthy, 2004). However, 1 day later estradiol levels had decreased in most brain regions and only the hypothalamus maintained a sex difference. It should be noted, however, that measurable concentrations of estradiol were consistently present neonatally in the female hypothalamus/preoptic area, a finding that is consistent with a role for estradiol in promoting the development of female-typical characteristics of neural structure and function.

Second, the critical period for female neural development may occur later than that for male neural development. Other research (Quadros, Goldstein, De Vries, & Wagner, 2002) showed that male-typical levels of progesterone receptor (PR) expression in the hypothalamus of rats developed prenatally under the influence of estrogens, whereas a female-typical increase in PR levels in the hypothalamus, probably induced by ovarian estrogens, was observed during the second postnatal week. Similar results were obtained using ArKO mice (Brock, Douhard, Baum, & Bakker, 2010); the male-typical pattern in PR expression develops prenatally under the influence of estradiol whereas the female-typical pattern in PR expression develops postnatally (after day 10 after birth), also under the influence of estradiol. These results thus suggest a critical period for estradiol-induced female development during the postnatal period. This is in line with the results obtained in female AFP-KO mice (Bakker et al., 2006) which clearly showed that a principal action of prenatal estrogen action in the brain is to defeminize the capacity to display feminine sexual behavior later in life. Thus, if estrogens actively feminize the female brain, they have to do so during the postnatal period when levels of alpha-fetoprotein have become insignificant. Indeed, it was found that treatment with estradiol over a specific postnatal period (day 15–25) restored lordosis behavior in female ArKO mice to levels observed in wild-type females (Brock, Baum, & Bakker, 2011).

Taken together, results obtained in AFP-KO and ArKO mice suggest that estradiol can have both defeminizing and feminizing actions on the brain depending on when during development estradiol is available. The defeminizing actions of estradiol normally occur prenatally in males and are avoided in fetal females because of the protective actions of alpha-fetoprotein, whereas the feminizing actions of estradiol normally occur prepubertally in genetic females, when the ovaries start to produce estrogens, i.e., in the second week after birth, and when circulating concentrations of alpha-fetoprotein have diminished so that it no longer plays a protective role. These results also suggest a differential role for brain versus ovarian aromatase in the sexual differentiation of the brain. The ovary is most likely the source of estradiol in the female since the development of female-typical neural and behavioral characteristics coincides with increased secretion of estradiol by the ovary. By contrast, the brain is the most likely source of estradiol in the male since the testes do not show any significant aromatase activity and any estradiol produced by the testes will be bound to alpha-fetoprotein and thus not available for the brain.

1.6 Sex Differences in the Brain in Relationship to Sexual Behavior and Sexual Orientation

Although an important role of testosterone and/or its metabolite estradiol in inducing a male-typical organization of the brain is no longer doubted, the particular cells and genes on which these sex hormones act during development to initiate these events still need to be uncovered. At present, many sex differences have been described in the nervous system, in particular in the hypothalamus, a brain structure at the base of the brain that is essential in reproduction since it controls both sexual behavior and the secretion of pituitary hormones and thus gonadal function. Lesions in discrete regions of the anterior hypothalamus (AH), such as the preoptic area (POA), eliminated virtually all male copulatory behaviors in almost all vertebrate species studied to date (reviewed in Meisel & Sachs, 1994). In many species, including humans, the POA contains sexually dimorphic structures, such as the sexually dimorphic nucleus (SDN) in the rat (Gorski, Gordon, Shryne, & Southam, 1978) or the male nucleus in the ferret (Tobet, Zahniser, & Baum, 1986), which are visibly larger in males than in females and which are organized by gonadal hormones during early development. Several animal studies have linked heterosexual preferences in males to the presence of this male-typical nucleus in the POA/AH. Thus, lesions of the male nucleus in ferrets (Paredes & Baum, 1995) or the SDN in rats (Paredes, Tzschentke, & Nakach, 1998) changed males' sexual preferences from opposite-sex to same-sex partners. Perhaps the most convincing evidence for a role of this brain area and consequently fetal hormone exposure in sexual preferences comes from studies in sheep (Roselli, Larkin, Resko, Stellflug, & Stormshak, 2004). About 8 % of rams prefer to approach and mount other rams as opposed to ewes. This homosexual preference is persistent in these rams, i.e., they do not change into a heterosexual preference during their lifespan. In sheep, like in rats and ferrets, a sexually dimorphic cell group of cells exist in the POA/AH (ovine SDN) which is significantly larger in males than females and which is organized perinatally by estradiol formed from testicular testosterone. Interestingly, the volume of this ovine SDN was twice as large in "heterosexual" as in "homosexual" rams, begging the question of whether there is a causal link between the size of the ram's sexually dimorphic POA/AH nucleus and the motivation to seek out an opposite-sex mating partner.

1.6.1 Sex Differences in the Brain in Relationship to Partner Preferences ("Sexual Orientation"): Role for Olfaction

In many animal species, the preference for an opposite-sex partner depends critically on the sense of smell. For example, ferrets that were made anosmic no longer showed any partner preferences for the opposite sex even though subjects could see, hear, and interact physically with the stimulus ferrets (a sexually receptive female and a sexually active male; Kelliher & Baum, 2001). This finding is quite remarkable since, in contrast to rodent species which are mostly nocturnal, the diurnal ferret has a well-developed visual system, and adult male ferrets are typically twice as large as adult female ferrets. Furthermore, odors (which have traditionally been classified as pheromones) have also been shown to induce important neuroendocrine changes which affect several aspects of reproduction (Lombardi & Vandenbergh, 1977; Whitten, 1959). These neuroendocrine effects of pheromones are mediated by gonadotropin-releasing hormone (GnRH) neurons (~800 neurons) that are found scattered in the AH and adjacent areas (Silverman, Livne, & Witkin, 1994). These neurons secrete GnRH, a decapeptide that stimulates the release of gonadotropins [luteinizing hormone (LH) and follicle-stimulating hormone (FSH)] from the pituitary. The gonadotropins act on the gonads, regulating gametogenesis, steroidogenesis, and estrous cycling. Interestingly, brain injections of GnRH can stimulate sexual behaviors in both male and female rodents, suggesting that GnRH neurons also participate in the neural circuits that control these behaviors.

Vertebrates have evolved dual olfactory systems, which differ in their anatomy, central projections, and function (Keverne, 2004). The main olfactory system can detect an almost infinite variety of odors derived from both the inanimate ecological and social environments. In addition, rodents possess an accessory (vomeronasal) olfactory pathway which links directly with limbic brain structures such as the amygdala and the hypothalamus (POA/AH) (Scalia & Winans, 1975). It is generally believed that recognition of the opposite sex involves the main olfactory pathway and that the vomeronasal system, through its close connections with the hypothalamus and in particular with the GnRH system, is the primary pathway for bringing about neuroendocrine changes. In fact, there is a clear anatomical link between the vomeronasal pathway and the GnRH system since GnRH neurons originate at the same time in development as neurons from the vomeronasal organ (VNO) in the olfactory placode (Schwarting, Wierman, & Tobet, 2007). Thus, sex differences in the VNO projection pathway are laid down at the same time as sex differences in the GnRH neural system. Accordingly, pheromones have been shown to activate the VNO projection pathway, including the peripheral VNO and the accessory olfactory bulb (AOB), as well as its downstream target-sides including the POA/AH in a sexually dimorphic manner in mice and rats. This suggests that a sexually dimorphic processing of pheromones may contribute to sex differences in sexual attraction and sexual orientation.

1.7 Sexual Differentiation of the Human Brain

An important question is that if steroids play such a pivotal role in masculinizing the brains of nonhumans, do they also have the same function in our own species? Do men and women behave differently because males are exposed to more testosterone prenatally? Most clinical evidence suggests that testosterone, indeed, induces male-typical psychosexual differentiation in men prenatally (Baum, 2006; Swaab, 2007). The strongest clinical evidence derives from syndromes in genetic males (46, XY) with either cloacal exstrophy or complete androgen receptor insensitivity (CAIS) due to a mutation of the androgen receptor gene. In both syndromes individuals have been assigned as female at birth despite having testes that produced normal, male levels of testosterone during fetal development. A notable occurrence of gender dysphoria and gender role switching from female to male in adolescence and adulthood is observed in individuals with XY cloacal exstrophy, whereas this is not the case in CAIS individuals, in whom all tissues, including the brain, are insensitive to testosterone. Furthermore, genetic women (46, XX) with congenital adrenal hyperplasia (CAH), who have been exposed prenatally to excessive androgens, present an increased incidence of bisexual orientation and gender dysphoria (Meyer-Bahlburg, Dolezal, Baker, & New, 2008). In contrast with rodent studies, there is little evidence for a role of estradiol in the sexual differentiation of the human brain since men with either a mutation in the estradiol receptor or aromatase gene have a normative male-typical gender identity (Baum, 2006).

Another important but more elusive question is whether prenatal steroids masculinize the human brain with respect to sexual orientation. Does testosterone that masculinizes the human body also masculinize the fetal brain so that, in adulthood, this person will be attracted to women? One strategy has been to find somatic markers that correlate with levels of prenatal androgens and to ask whether they also covary with sexual orientation. For instance, eyeblink patterns, otoacoustic emissions (clicks emanating from the ears), and measures of fingers and digit ratios all suggest that lesbians, on average, are exposed to more prenatal androgen than heterosexual women (Morris, Jordan, & Breedlove, 2004). However, all these studies remain correlative since they do not provide a direct relationship between prenatal testosterone and sexual orientation in adulthood. So far, animal studies have helped by framing the questions about the origins of human sexual orientation. For instance, studies of the rat SDN have inspired examination of the human POA, where a similar sexually dimorphic nucleus was observed [SDN or interstitial nucleus of the anterior hypothalamus (INAH-1 and 2)] which is larger in men than in women. However, no variations in the size of this nucleus have been observed in relation to sexual orientation (Swaab, 2007). In addition, three independent groups have shown that a different nucleus in the AH, INAH-3, is significantly larger in heterosexual men than women (Allen, Hines, Shryne, & Gorski, 1989; Byne et al., 2001; LeVay, 1991) and, in a highly publicized study (LeVay, 1991), it was reported that the volume of INAH-3 was greater in heterosexual than in homosexual men, although this latter finding still awaits full replication (Byne et al., 2001). Both human and animal studies suggest that it is likely that the POA/AH plays an important role in determining sexual orientation.

Animal studies can be used to validate results obtained in humans. For example, Swaab and Hofman (1990) observed that the suprachiasmatic nucleus (SCN), the clock of the brain, was twice the size in homosexual men compared to heterosexual men. In an experiment with rats, a similar difference could be induced by blocking the conversion of testosterone to estradiol using the aromatase inhibitor ATD around the time of birth (Swaab et al., 1995). This experiment yielded “bisexual” rats that had greater cell numbers in their SCN, indicating that the difference in SCN size between homo- and heterosexual men might be caused by alterations in sex hormone action during early development.

By contrast, meaningful animal models of human gender identity have not been forthcoming since gender identity is uniquely human. Thus, in the absence of adequate animal models or hints, we are basically left with the phenomenon of men and women suffering from gender identity disorders (GID), also known as transsexual people, to study the origins of gender identity in humans. The finding (Zhou, Hofman, Gooren, & Swaab, 1995) of a sex reversal in the size of the central nucleus of the bed nucleus of the stria terminalis (BSTc) in male-to-female transsexuals is intriguing and suggests the implication of sex hormones in gender identity.

1.7.1 The Role of Estradiol in the Development of the Female Human Brain

Recent studies in mice have shown that female-typical neural and behavioral characteristics develop under the influence of estradiol during a specific prepubertal period (Brock et al., 2010, 2011). These results thus challenged the classical view of a default organization of the female brain. To date, in humans, there is only evidence for a role of testosterone in the development of the human brain based on clinical syndromes such as CAIS and CAH. In addition, whether alphafetoprotein actually binds estradiol in humans, as has been shown in rodents, is still matter of debate. This might not be relevant for the sexual differentiation of the human brain. The female brain might not need to be protected from estradiol as no clear role for estradiol in the development of male-typical characteristics (at least regarding gender identity) has been found. Men with either a mutation in the estradiol receptor or aromatase gene have a normative male-typical gender identity (Baum, 2006). However, there is some evidence that estradiol might play a role in the development of the female brain. Several studies (Downey, Ehrhardt, Gruen, Bell, & Morishima, 1989; Rolstad, Moller, Bryman, & Boman, 2007; Shaeffer, Lange, & Bondy, 2008) have shown that women with Turner syndrome (TS), a disorder in which all or part of one X chromosome are missing with ovarian dysgenesis as one of several morphological consequences, reported significantly lower heterosexual function (e.g., ever engaging in genital petting or sexual intercourse, ever having had a boyfriend) than control women. Furthermore, Ross, Roeltgen, Feuillan, Kushner, and Cutler (1998) reported some beneficial effects of prepubertal low-dose estrogen treatment on cognitive function. Twenty-four TS girls exhibited a significant improvement in their motor function and nonverbal processing speed after estradiol treatment, when compared to their TS peers who received a placebo treatment. Clearly more research is needed to determine whether estradiol feminizes the brain in humans.

1.7.2 Sex Differences in the Brain in Relationship to Sexual Orientation: Role of Olfaction in Humans

Human olfaction remains poorly understood, relatively. This might be due to the low value people place on smelling in the first place. However, the human nose is, in fact, the main organ of taste as well as smell. The taste buds on our tongues can only distinguish four qualities—sweet, sour, bitter, and salty—all other “tastes” are detected by the olfactory receptors high up in the nasal passages. Another possible explanation for the lack of knowledge on olfaction in humans is that it is generally thought that humans are not able to smell very well, at least not in comparison with many animal species, and that olfaction does not play an important role in our social and sex life (more on this below). Although the human sense of smell is feeble compared to that of many different animal species, it still can be acute. We are able to recognize thousands of different odors, and we are able to detect odors even in very small quantities. Interestingly, there is an important sex difference in odor sensitivity: women consistently outperform men on all tests of smelling ability. This sex difference is actually also observed in several animal species, such as mice, rats, and pigs.

In contrast with many animal species, the presence of a vomeronasal organ in humans has been subject of debate. Although a vomeronasal organ has been demonstrated in human embryos (Tirindelli, Dibattista, Pifferi, & Menini, 2009), this structure becomes more simplified later in development, and in adult life only a blind-ended diverticulum in the septal mucosa can be found. Furthermore, the epithelium lining the vomeronasal organ differs from that of other species. Several studies have shown that vomeronasal cells do not express olfactory marker protein in humans which is used as a general marker since it is expressed abundantly in olfactory and vomeronasal sensory neurons in other species (Tirindelli et al., 2009). Likewise, no vomeronasal nerve bundles could be identified using histological methods; thus, even if any of these vomeronasal neurons might be chemosensitive, it is questionable how they would communicate with the brain. Accordingly, no accessory olfactory bulb has been identified in the human olfactory bulb. Thus, it seems that the development of any human vomeronasal structures is limited to the embryonic stage.

Since humans do not appear to possess a functional accessory olfactory system, the role of pheromones in human social and sexual functioning has always been questioned. It has classically been thought that any pheromonal action that induces physiological and neuroendocrine changes is mediated by the vomeronasal system. So for many scientists, it was clear that there would be no pheromonal action in humans since there is no vomeronasal system. However, rodent studies have shown that the main olfactory system is also involved in the detection and processing of certain chemosignals leading to physiological and behavioral changes. Thus, if there is any pheromonal action in humans, these chemosignals must be processed through the main olfactory system. At present, there are some examples of pheromonal action in humans and the list is getting longer. For example, it has been demonstrated that exposing women to axillary extracts from women in the follicular phase of their menstrual cycle shortens the length of the recipient's menstrual cycle (Stern & McClintock, 1998). In addition, exposure to male axillary extracts induces changes in luteinizing hormone pulses and mood in women (Preti, Wysocki, Barnhart, Sondheimer, & Leyden, 2003). The androgenic steroid, androstadienone, which can be found in sweat, blood, and semen in higher concentrations in men than in women, has been proposed to be a "putative male pheromone." Using positron emission topography (PET), it was reported that heterosexual women who were exposed to the crystalline form of this steroid had activation in the hypothalamus, whereas heterosexual men only had activation in brain areas related to odor processing, such as the amygdala, piriform cortex, insula, and orbitofrontal cortex (Savic, Berglund, Gulyas, & Roland, 2001). Interestingly, homosexual men also had hypothalamic activation when exposed to androstadienone (Savic, Berglund, & Lindstrom, 2005), but not lesbian women (Berglund, Lindstrom, & Savic, 2006), suggesting that it may signal mate attraction in humans. However, these studies have been criticized for the fact that subjects were exposed to the crystalline form of the steroid, which might not represent anything biologically relevant, since the concentration used is not comparable to any that is actually going to be excreted in the human armpit. A recent study (Burke, Veltman, Gerber, Hummel, & Bakker, 2012) actually showed that both men and women showed a hypothalamic activation upon smelling androstadienone, but that this activation was dependent on the concentration of the odorous steroid. Thus, more research is needed to more thoroughly analyze possible behavioral and/or physiological actions of this compound in heterosexual men, either in the context of male–male or of male–female interactions.

In summary, even though neurobiological research regarding sexual behavior, including gender identity and sexual orientation, in humans is still in its nascency, the mechanisms underlying the sexual differentiation of the brain seem to be quite similar between animals and humans: testosterone induces male-typical neural and behavioral characteristics during early development. However, more research using neuroimaging techniques, as well as postmortem research, is necessary to increase our understanding of the organizing and activating roles of sex hormones on the brain and behavior in humans and especially their effects on the development of gender identity.

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Chapter 2
Genetic Aspects of Gender Identity Development and Gender Dysphoria

Daniel Klink and Martin Den Heijer

Abstract The development of gender identity, its variance, and gender dysphoria is thought to be a complex process involving biological and psychosocial factors. Heritability studies have demonstrated a genetic factor for the development of gender dysphoria. The brain is regarded as the anatomical substrate of gender identity, and sex differences of the brain are studied to elucidate the process of gender identity development. Many sex differences have been attributed to hormonal action, and the first genetic studies in transsexuals were focused on sex-steroid-related genes. To this day, a convincing candidate gene has not been identified, and it is now known that sex chromosomes have a direct effect on sex differentiation and that they may play a role in gender identity development. For future studies of the genetic base of gender dysphoria, new techniques, such as genome-wide studies, have become available. In addition, epigenetic studies may provide for a different association perspective of the genetics of gender dysphoria.

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2.1 Introduction

Gender identity development is a complex developmental process that is thought to be influenced by biological factors (such as hormonal and genetic factors) and psychosocial factors which also interact with each other. Gender identity is one of the most remarkable sex differences in humans. The brain is regarded as the anatomical substrate of gender identity, and numerous studies investigating gender identity development and variations in development, i.e., gender dysphoria, use sex differences of the brain as a proxy for gender identity. In Chap. 1 the role of (gonadal) hormones is addressed in mostly animal models, using behavioral outcome measures to evaluate sex differentiation in either feminine or masculine directions. In Chap. 3 the psychological factors that contribute to gender identity development are presented. In this chapter the contribution of genetics to gender identity and gender dysphoria is explored with a focus on the brain and its sex differences.

Sex differences in the human brain are prominent and have important implications for each sex, as they uniquely affect biochemical processes, may contribute to the susceptibility to specific diseases, and may influence specific behavior. These differences manifest themselves in a variety of ways, both structural and functional. In human brains there are region-specific dimorphisms with some structures larger in females (caudate nucleus, hippocampus, Broca's area, anterior commissure, and right parietal lobe) and some larger in males (hypothalamus, stria terminalis, and amygdala) (Goldstein et al., 2001). In addition to neuroanatomical differences, males and females exhibit different patterns in neurochemistry, the transmission, regulation, and processing of biomolecules involved in neurosignaling (Ngun, Ghahramani, Sanchez, Bocklandt, & Vilain, 2011). For example, men are more sensitive to cholinergic stimulation of the hypothalamic–pituitary–adrenal cortisol axis than women (Rubin, Sekula, O'Toole, Rhodes, & Czambel, 1999). Besides biological differences, men and women differ in many psychological and behavioral aspects; men perform better on specific visuospatial tasks (e.g., mental rotation) (Voyer, Voyer, & Bryden, 1995) and mathematical problem solving (Benbow, Lubinski, Shea, & Eftekhari-Sanjani, 2000). Women do better on verbal fluency, articulation, and verbal memory tests (Becker, 2008).

Of interest with respect to gender identity and gender dysphoria are the findings that male-to-female (MtF) transsexuals have some sex-specific brain characteristics more similar to females than males. Two sex-dimorphic nuclei, the central portion of the bed nucleus of the stria terminalis (BSTc) and the interstitial nucleus of the anterior hypothalamus 3 (INAH3), located in the hypothalamus, appear to be female sized and thus smaller when compared to men (Garcia-Falgueras & Swaab, 2008; Zhou, Hofman, Gooren, & Swaab, 1995). However, it is still unclear what their role is in the development of gender identity. The MtF subjects in which the BSTc was studied received estrogens prior to their demise, and thus a hormonally mediated effect could not be excluded (Zhou et al., 1995). On the other hand, in terms of INAH3, it was postulated that since the INAH3 did not differ between premenopausal and postmenopausal women, the feminization of the INAH3 in MtF transsexuals was not due to estrogen treatment. It was implied that the INAH3 is at least partly a marker of an early atypical sexual differentiation of the brain and that the changes in INAH3 and the BSTc may belong to a complex network that may structurally and functionally be related to gender identity (Garcia-Falgueras & Swaab, 2008; Zhou et al., 1995).

These two reports illustrate the complexity of sex differentiation investigation and its potential pitfalls. Sex differences are well described, but the underlying mechanisms of development are not explained. As reviewed in Chap. 1, the role of (gonadal) hormones has been extensively researched in (mostly) animal models, paving a path for further exploration of hormonal influences on sex differentiation in humans. In this respect, the candidate genes pursued in past genetic studies of transsexuals are involved in sex steroid synthesis or action. In addition to hormonally mediated effects, more data nowadays have emerged of effects on sex differentiation that are not due to hormonal action but arise from expression of X and Y genes within non-gonadal cells and result in sex differences in the functioning of those cells (Ngun et al., 2011).

In this chapter we will first review the studies with transsexual populations, in search of genetic factors. The first approach is to establish whether heritable factors play a role in gender dysphoria development in heritability studies. The next step is to identify those factors found in studies exploring the association of gender dysphoria and sex-steroid-hormone-related genes. Subsequently, we will address direct (i.e., not hormonally mediated) genetic effects on sex differentiation and so present a novel concept of sex differentiation, as proposed by Arnold (2009b). Finally, we will discuss future directions of genetic research of gender dysphoria. New techniques have become available such as genome-wide association studies, which may have a place in the quest for the genetic base of gender identity development and gender dysphoria. In addition, the emerging field of epigenetics—the study of stable alterations in gene expression potential that arise during development, differentiation, and under the influence of the environment—may offer new insights as epigenetic mechanisms may be mediators between sex and its differentiation and genetic base.

2.2 Heritability Studies of Gender Dysphoria

The first step in studying genetic factors in gender dysphoria is to investigate the extent to which gender dysphoria can be attributed to genetic factors or to environmental factors (including hormonal levels during early development and psychosocial factors). Heritability studies provide answers to the question of whether a certain biological or psychological trait is heritable. Twin studies are a good example of this kind of design. If a certain trait is more concordant in monozygotic twins compared to dizygotic twins, this strongly indicates that such a trait is heritable. The measure of heritability is expressed as the part of the variance that is explained by shared genes relative to the total variation and varies from 0 to 1, where 0 means that there is no genetic explanation for a trait and 1 that it is completely determined by genetic factors. Although this heritability index could also be assessed from family studies, most of the studies regarding gender dysphoria are done in twins.

The first heritability study is the one by Lippa and Hershberger (1999). They analyzed data from Loehlin and Nichols' (1976) classic twin study that recruited 839 same-sex pairs of twins who were high school juniors (ages 16–17) from the USA. They used several scales of masculinity–femininity including "gender diagnosticity," which refers to the Bayesian probability that an individual is predicted to be masculine or feminine based on gender-related interests. The estimated within-sex heritability of gender diagnosticity was 0.53, which indicates a moderate to high measure of heritability. Later, Loehlin and colleagues applied the same method to a larger cohort of five studies and found that gender diagnosticity is moderately heritable (somewhere between 25 and 47 % of the total variance) (Loehlin et al., 2005).

In 2000, Bailey and colleagues reported a heritability pattern for childhood gender nonconformity in 1891 adult twins. They found heritability estimates of 0.50–0.57 in men and 0.37–0.40 in women. This study focused on childhood gender nonconformity as a heritable component of adult sexual orientation and was performed in an adult population (median age 29 years) which can involve a considerable recall bias (Bailey, Dunne, & Martin, 2000).

In 2002, Coolidge and colleagues published a study of 314 twins (96 monozygotic and 61 dizygotic twins; mean ages 4–17 years) on the heritability of gender identity disorder. Gender identity disorder (GID) was assessed by a 6-item GID scale, based on DSM-IV criteria for GID and ranging from 4 to 24. A score of 15 or higher indicates a high likelihood for a clinical diagnosis of GID. The prevalence of clinically significant GID symptomatology in the twin sample was estimated to be 2.3 %. The model that best described the data included a significant additive genetic component accounting for 62 % of the variance, suggesting that there is a strong heritable component to GID. The effects were stronger in the older (11–17) than in the younger group (4–10). In this study the scoring of GID symptoms was done by the mother and thus might have some bias based on the type of twins (Coolidge, Thede, & Young, 2002).

In 2005, Knafo and colleagues reported a study in 5,799 twin pairs, between ages 3 and 4, for which parents rated their twin children's masculinity and femininity. Boys were selected as gender atypical if they were highly feminine relative to other boys, and girls were selected if they were highly masculine relative to other girls. Among fully gender atypical children (e.g., feminine boys also low on masculinity), heritability estimates were 0.21 in boys and 0.74 in girls (Knafo, Iervolino, & Plomin, 2005).

Van Beijsterveldt, Hudziak, and Boomsma (2006) studied the genetic and environmental influences on cross-gender behavior in twins at the age of 7 years ($n \sim 14{,}000$ twins) and 10 years old ($n \sim 8{,}500$ twins). The behavior was assessed by maternal report that the child behaves like or wishes to be the opposite sex. The prevalence was 3.2 % and 5.2 % for 7-year-old boys and girls, respectively, and decreased to 2.4 % and 3.3 % for 10-year-old boys and girls. Heritability estimates were 0.77 at age 7 and 0.71 at age 10 (Van Beijsterveldt et al., 2006).

Burri, Cherkas, Spector, and Rahman (2011) published a study in 4,426 British female twins focusing on sexual orientation, childhood gender typicality, and adult gender identity. The scale for adult gender identity was based on items such as "I don't feel very masculine" and "I pride myself on being feminine." Heritability for this scale was only 0.11 indicating a low influence of genes, which the authors attributed to a substantial measurement error (Burri et al., 2011).

Most studies have reported a considerable heritability of gender-related traits within sexes. However, a key question is whether these estimates provide an accurate impression of the heritability of gender dysphoria. Most of the studies focused on masculinity and femininity traits and do not include criteria for dysphoria. Only Coolidge's study used a questionnaire based on DSM-IV criteria for gender identity disorder (Coolidge et al., 2002). Van Beijsterveldt's study was based on two items of which one refers to "behaves like opposite sex" and the other "wishes to be of opposite sex" (Van Beijsterveldt et al., 2006). Another point of concern is that some studies were conducted with very young children, and it is not clear whether gender nonconforming behavior at very young ages corresponds to gender dysphoria during adolescence or adulthood.

Recently one paper reported data on twins of which one was diagnosed with gender identity disorder (Heylens et al., 2012). Of the 23 monozygotic female and male twins, 9 (39.1 %) were concordant for GID; in contrast, none of the 21 same-sex dizygotic female and male twins were concordant for GID. Although the sample size was rather low, this indicates a role for genetic factors in the development of GID.

2.3 Candidate Genes Involved in Gender Identity Development and Gender Dysphoria

A small number of candidate genes have been studied for gender dysphoria. Since conceptual frameworks determine experimental designs, the predominance of the classical theory of brain and behavioral sexual differentiation (see Chap. 1) presumably has led to investigations of genes that are involved in the biosynthesis of sex steroids or mechanisms of action. Assuming a pivotal role for sex hormones on sex differentiation of the brain and thus gender identity development and its variations, alterations in hormone levels or activity may contribute to the development of gender dysphoria. Therefore, the reported studies were aimed to identify differences in genes between transsexuals and the reference population. In this section we review these investigations. First, the production of steroid hormones and their physiological mode of action are briefly reviewed. Second, we discuss the genetic base of enzymes in these processes and how individuals are affected by either faults (i.e., mutations) or variants (i.e., polymorphisms). Finally, the outcome of association studies of sex-steroid-related genes in transsexuals is discussed.

2.3.1 Sex Steroid Biosynthesis and Mechanisms of Action

Steroidogenesis, the production of steroid hormones, mainly takes place in the gonad and adrenal gland. Cholesterol is the common precursor and is stepwise converted into biologically active steroid hormones. Several enzymes are needed to catalyze each step of the steroidogenesis. First, cholesterol is converted into pregnenolone (Miller & Auchus, 2011). Pregnenolone subsequently can be further used by $P450c_{17}$ (steroid 17-alpha-hydroxylase). This enzyme mediates both 17-alpha-hydroxylase and 17,20-lyase activity and allows the adrenal glands and gonads to synthesize both 17-alpha-hydroxylated glucocorticoids (via 17-alpha-hydroxylase activity) and sex steroids (via 17,20-lyase activity) (Chung et al., 1987; Kagimoto, Winter, Kagimoto, Simpson, & Waterman, 1988; Van Den Akker et al., 2002). In the latter, DHEA is produced. Like many other steroidogenic enzymes, steroid 17-alpha-hydroxylase is a form of cytochrome P450 (Miller, 2005). DHEA can be converted into androgens, namely, androstenedione and—via androstenediol—testosterone. The actions of androgens are mediated by the androgen receptor. This ligand-dependent transcription factor belongs to the superfamily of nuclear receptors. All members of this family share similar characteristics; these include a separate hormone-binding domain, a high-affinity DNA-binding domain, a tendency to form dimers (a structure built out of two equal molecules), and an enhanced affinity for the cell nucleus in the presence of bound hormones. Only one androgen receptor has been identified and cloned, despite the two different ligands, testosterone and dihydrotestosterone (Miller, 2005; Trapman et al., 1988). The irreversible conversion of testosterone into the more potent androgen, dihydrotestosterone, is catalyzed by 5-alpha-reductase type II (SRD5a2). The receptor–ligand complex translocates into the nucleus, where it transactivates genes with androgen-responsive elements resulting in the development of the male external genitalia, urethra, and prostate during embryogenesis. In addition, it is responsible for most androgen-mediated events of male sexual maturation at puberty (Wilson, Griffin, & Russell, 1993).

On the other hand, cP450arom (aromatase) is the enzyme that catalyzes the synthesis of estrogens from androgens. Therefore, the activity of this enzyme complex affects both androgen metabolism and estrogen synthesis. The biological importance of the aromatase complex is related not only to its role in the synthesis of estrogens but also to its potential influence on the balance of the androgen–estrogen ratio in different tissues (Belgorosky, Guercio, Pepe, Saraco, & Rivarola, 2009). Estrogen effects are exerted by the estrogen receptors (ERs), members of the steroid receptor family. To date, two ER subtypes have been cloned, called ERα and ERβ (Kuiper, Enmark, Pelto-Huikko, Nilsson, & Gustafsson, 1996). Progesterone can be directly derived from pregnenolone and is produced by the corpus luteum, a temporary endocrine structure in women involved in the menstrual cycle and pregnancy. It plays a central role in the reproductive events associated with the establishment and maintenance of pregnancy. The progesterone receptor (PGR), a member of the steroid receptor superfamily, mediates the physiologic effects of progesterone (Akison & Robker, 2012).

2.3.2 Disorders and Polymorphisms of Steroidogenic Enzymes and Steroid Receptors

The information to synthesize steroidogenic enzymes and steroid receptors is stored in genes. Genes are made from a long molecule called DNA, which is copied and inherited across generations. The information is encoded in the DNA sequence (genetic code), which allows the genetic machinery to read the information in the genes in triplet sets of codons. The DNA sequence of a given gene consists of parts that are translated, i.e., used to construct the gene product, called exons. In addition, between exons are parts that are not translated, the so-called introns, which may have regulatory functions. Each unique form of a single gene is called an allele. Mutations are random changes in genes and can create new alleles. Mutations can produce new traits but also can cause disease when it leads to dysfunction of the encoded product. In addition, there are natural variations in a gene, DNA sequence, or chromosome, called polymorphisms, which have no adverse effects on the individual and occur with fairly high frequency in the general population. The most common type of polymorphism involves variation at a single base pair which leads to a single-nucleotide polymorphism, or SNP (pronounced “snip”). Each SNP represents a difference in a single DNA building block, called a nucleotide. For example, an SNP may replace the nucleotide cytosine (C) with the nucleotide thymine (T) in a certain stretch of DNA. SNPs occur normally throughout a person’s DNA. They occur once in every 300 nucleotides on average, which means there are roughly ten million SNPs in the human genome. Most commonly, these variations are found in the DNA between genes. They can act as biological markers to locate genes that are associated with disease. When SNPs occur within a gene or in a regulatory region near a gene, they may play a more direct role in disease by affecting the gene’s function. Most SNPs have no effect on health or development. Some of these genetic differences, however, have proven to be very important in the study of human health. SNPs may help predict an individual’s response to certain drugs, susceptibility to environmental factors such as toxins, and risk of developing particular diseases, such as heart disease, diabetes, and cancer. Polymorphisms can also be much larger in size and involve long stretches of DNA (Cargill et al., 1999).

2.3.2.1 Steroidogenic Enzymes: Disorders and Polymorphisms Studied in the Transsexual Population

Faults, i.e., mutations in sex-steroid-related genes can lead to disorders of sex development (DSD). Herein, the sex differentiation of the genitals, both external and internal, may become ambiguous. Polymorphisms have a less profound effect. In this and the next paragraph, the genes which were studied in the transsexual population are reviewed. We use the term “transsexual” to refer to persons with extreme gender dysphoria who pursue sex reassignment, thus not to all people with gender dysphoria per se. The normal gene structure is discussed per gene first and then followed by mutations causing DSD. Finally, we review the polymorphisms studied and how they may relate to transsexualism.

Pc450$_{17}$

The Pc450$_{17}$ (CYP17) gene was mapped to chromosome 10q24.3 (Fan et al., 1992). Mutations causing complete combined 17-alpha-hydroxylase and 17,20-lyase deficiency led to incapacity to produce androgens and thus result in 46XY individuals with female external genitalia (Auchus & Miller, 2012). An SNP has been identified (CYP17A2T>C SNP) (Carey et al., 1994) and is associated with elevated plasma levels of estradiol and progesterone (Feigelson et al., 1998). Estradiol and progesterone have been shown in rodents to play a role in sex differentiation of the brain (Menger, Bettscheider, Murgatroyd, & Spengler, 2010), and it is therefore of interest to study this gene in both FtM and MtF transsexuals.

5-Alpha Reductase (SRD5*a2)*

The SRD5a2 gene maps to chromosome 2p23 and spans over 40 kb of genomic DNA, containing 5 exons and 4 introns, and encodes a 254 amino acid protein (Labrie et al., 1992). Mutations in the gene causing deficiency will lead to hypovirilization in 46XY individuals (Andersson, Berman, Jenkins, & Russell, 1991). Several polymorphisms are known and have been associated with medical conditions such as polycystic ovaries (Graupp, Wehr, Schweighofer, Pieber, & Obermayer-Pietsch, 2011) and prostate cancer (Li, Coates, Gwinn, & Khoury, 2010). The SRD5A2 V89L SNP in codon 89 of exon 1 causes a replacement of the amino acid valine with leucine and has been shown to result in almost 30 % reduced enzyme activity and thus lower concentration of testosterone metabolites (Makridakis et al., 1997). It was found to be overrepresented when hypospadia cases were compared to normal controls (Thai et al., 2005). Therefore, this polymorphism may be associated with hypovirilization of other organs, i.e., the brain and thus with gender dysphoria.

Aromatase (cP450arom)

In humans, cP450arom is the product of a single gene—*CYP19*—located on chromosome 15q21.1. The protein-coding sequence is contained within nine exons (2–10), in which translation, initiation, and termination codons are present, and spans approximately 35 kb of DNA. There are multiple first exons that are not translated but are involved in tissue-specific expression. Several promoters are found within a 90-kb region upstream of the coding region (Means et al., 1989). cP450arom is expressed in a number of tissues, including parts of the placenta, gonads, and brain (including the hypothalamus, hippocampus, and amygdala), and is subjected to multifactor regulation by a diverse group of hormones and factors that differ markedly between tissues (Belgorosky et al., 2009).

Clinical presentation of aromatase deficiency is different in 46XX and 46XY individuals. Males (46XY) typically present after puberty with prolonged linear growth and tall stature, reduced bone mineralization, impaired fertility, insulin insensitivity, and dyslipidemia. Females (46XX) usually present at birth with ambiguous genitalia. In normal conditions aromatase protects the female fetus from adrenal-derived androgens. When aromatase is deficient, the fetus will be exposed to increased levels of androgens, resulting in virilization of the external genitalia. In one case, a 46XX individual was raised as a male and reported male gender identity, role, and orientation. The patient had spontaneous breast development that progressed to Tanner stage 4 at 14 years of age. A salpingo-oophorectomy and hysterectomy was performed (Lin et al., 2007). However, aromatase deficiency is rare, with fewer than 20 patients reported in the literature (Belgorosky et al., 2009).

A more common polymorphism was demonstrated in the fourth intron consisting of a (TTTA)n repeat (Polymeropoulos, Xiao, Rath, & Merril, 1991) and has been reported in association with variations in bone mineral density and fracture risk in both sexes (Masi et al., 2001; Van Pottelbergh, Goemaere, & Kaufman, 2003), breast (Dunning et al., 1999) and endometrial cancer (Berstein et al., 2001), and serum levels of sex steroids (Haiman et al., 2000). Also several SNPs were reported to be involved in hyperandrogenism in younger females (Petry et al., 2005). This suggests an important modulatory role for this enzyme in endocrine and metabolic function within the wider population. Aromatase is expressed in the brain of the human fetus (Montelli et al., 2012) and plays, as described in Chap. 1, a critical role in the differentiation of the developing brain in rodents (Roselli, Abdelgadir, & Resko, 1997). Therefore, CYP19 was an attractive candidate gene to study in the transsexual population.

2.3.2.2 Steroid Receptors: Disorders and Polymorphisms Studied in the Transsexual Population

Androgen Receptor (AR)

The AR gene is located on the X chromosome at Xq11. The gene consists of eight coding exons, and the structural organization is essentially identical to those of the genes coding for the other steroid hormone receptors (Brinkmann et al., 1989). A polyglutamine stretch, encoded by a polymorphic (CAG)*n*CAA repeat, is present in the NH_2-terminal domain (Sleddens, Oostra, Brinkmann, & Trapman, 1992). Variation in length (9–33 glutamine residues) is observed in the normal population. This polymorphism has functional significance, whereby the length of the CAG repeat is inversely proportional to the transcriptional activity of the androgen receptor (Palazzolo et al., 2008; Simanainen et al., 2011).

Androgen insensitivity syndrome is a disorder resulting from complete or partial resistance to the biological actions of androgens due to defective androgen receptor function. In complete androgen insensitivity syndrome, all tissues, including the brain, are unresponsive to testosterone, and the XY individual has a female phenotype and female gender identity. The clinical presentation of partial androgen insensitivity syndrome however depends on the degree of responsiveness of the external genitalia to androgens. The number of CAG repeats can have modulatory effects on the phenotypic manifestation of some mutations of the androgen receptor gene noted in partial androgen insensitivity syndrome, particularly when the phenotype varies with the same mutation (Palazzolo et al., 2008; Werner et al., 2006). In addition, it has been associated with several androgen-related disorders such as polycystic ovary syndrome (Lin, Baracat, Maciel, Soares, & Baracat, 2013), male infertility (Davis-Dao, Tuazon, Sokol, & Cortessis, 2007), prostate cancer (Gu, Dong, Zhang, & Niu, 2012), and even with growth during childhood in boys (Voorhoeve, van Mechelen, Uitterlinden, Delemarre-van de Waal, & Lamberts, 2011). Increased androgen insensitivity of the brain may play a part in the development of gender dysphoria, and therefore variation in length of the (CAG)*n*CAA repeat was investigated in transsexuals.

Estrogen Receptor (ER)

The two subtypes of ER are highly homologous in DNA and ligand-binding domains, but overall homology is only 55 %. Both subtypes are widely distributed throughout the body, each with distinct tissue and cell patterns of expression. The ERα mRNA expression appears to dominate in the hypothalamus and amygdala, indicating that the alpha-subtype might modulate neuronal cell populations involved in autonomic and reproductive neuroendocrine functions, as well as emotional interpretation and processing. In contrast, the hippocampal formation, entorhinal cortex, and thalamus appear to be ERβ-dominant areas, suggesting a putative role for ERβ in cognition, non-emotional memory, and motor functions (Osterlund, Gustafsson, Keller, & Hurd, 2000). ERα plays a critical role in regulating reproductive neuroendocrine behavior and function. ERβ appears to play an important role in nonreproductive behaviors, such as learning and memory, anxiety, and mood (Ter Horst, 2010).

ESR1 is the gene that codes for the ERα protein and is located on chromosome 6 (6q25.1). Transcription is regulated by multiple promoters that give rise to mRNA variants with distinct 5′-untranslated regions. These promoters are utilized in a tissue-specific manner resulting in different levels of expression of mRNA variants in individual tissues (Kos, Reid, Denger, & Gannon, 2001). The polymorphic $-1174(TA)_n$ repeat in promoter region of the *ESR1* gene has been associated with somatic conditions such as coronary heart disease, bone mineral density, familial premature ovarian failure, and endometriosis (Ascenzi, Bocedi, & Marino, 2006). The functional importance of these repeat nucleotide sequences has not been clarified although reports have suggested that these sequences, even when situated in the non-translated regions, may influence the expression of a gene (Zhang & Yu, 2007). In addition, this polymorphism has been associated with anxiety, neuroticism, psychoticism, antisocial behavior, and conduct disorder in humans (reviews in Sundermann, Maki, & Bishop, 2010; Westberg & Eriksson, 2008). ESR2 is located on chromosome 14 (14q23) and codes for ERβ. The CA repeat in the 3′ noncoding portion of the *ESR2* gene, c. 1092 + 3607(CA)$_n$, was suggested to be associated with bone mineral density in women (Ogawa et al., 2000) and with androgen and sex hormone-binding globulin (SHBG) levels. Women with relatively short repeat regions displayed higher hormone levels and lower SHBG levels than those with many CA repeats. In contrast, the TA repeat of the ER alpha gene did not have such an association (Westberg et al., 2001).

Progesterone Receptor (PGR)

The PGR gene is located on 11q21–q23 (Law et al., 1987) and uses separate promoters and translational start sites to produce two isoforms, PRA and PRB. Although PRA and PRB share several structural domains, they are distinct transcription factors that mediate their own response genes and physiologic effects with little overlap. PRB functions as a transcriptional activator in most cell and promoter contexts, while PRA is transcriptionally inactive and functions as a strong ligand-dependent transdominant repressor of steroid hormone receptor transcriptional activity. The first 140 amino acids of PRA contain an inhibitory domain (ID); deletion of the N-terminal 140 amino acids from PRA results in a receptor mutant that is functionally indistinguishable from PRB (Giangrande, Pollio, & McDonnell, 1997). The hPR gene has two promoters, regulating production of the hPR-B and -A protein isoforms. A +331G/A SNP was identified and is associated with an increased risk of endometrial cancer. Biochemical studies suggested that the +331G/A polymorphism increased transcription (De Vivo et al., 2002). A small (306-bp) insertion in intron G of the T2 allele of the human progesterone receptor was described and named "PROGINS" (Fuqua et al., 1991). Subsequently, two-point mutations were found to be linked to the PROGINS mutation. These two mutations included a G to T substitution in exon 4, causing a valine to leucine change (V660L), and a C to T substitution in exon 5 (H770H). These three variants of the progesterone receptor have been referred to in the literature as PROGINS complex (Agoulnik et al., 2004). Progesterone and PGR play an important role in the sexual differentiation of the rat brain. Numerous regions of the developing male rodent brain express PGR and show dramatic sex differences during critical windows of development, indicating a differential sensitivity of developing male and female brains to progesterone (Quadros & Wagner, 2008; Weisz & Ward, 1980).

2.3.3 Outcome of Association Studies of Sex-Steroid-Related Genes in Transsexualism

To date, only a few studies have investigated genes which may be related to the development of transsexualism. Two studies focused on one gene each (Bentz et al., 2007, 2008). Three studies comprised multiple genes, and therefore interactions between genes could be studied. Henningsson and colleagues (2005) were the first to report on sex-steroid-related genes and (only) male-to-female (MtF) transsexualism. The study population were 29 Caucasian MtF transsexuals and 229 healthy male controls. The second multiple gene study was done in 112 Caucasian MtF transsexuals from Victoria, Australia (76 subjects), and from Los Angeles (36 subjects). Healthy Caucasian males from Australia served as controls ($n = 258$) (Hare et al., 2009). The last study was done in Japan, in which 74 MtF and 168 FtM transsexuals were compared with 275 healthy age- and origin-matched controls (106 males and 169 females). All subjects were Japanese (Ujike et al., 2009).

The androgen receptor is an attractive candidate gene to investigate because a complete loss of function results in a 46XY female phenotype with a female gender identity. In addition, as previously described, the (CAG)*n*CAA-repeat polymorphism is known to have modulatory effects. Henningsson et al. (2005) demonstrated that the prevalence of a long (CAG)*n*CAA repeat is higher in MtF transsexuals. This preliminary finding was later confirmed in a larger cohort consisting of 112 Caucasian MtF transsexuals (Hare et al., 2009). However, the Japanese case control association study did not find a significant difference in the distribution of long and short (CAG)*n*CAA repeats (Ujike et al., 2009).

The CYP 19 (aromatase) polymorphism and ERβ polymorphism were also studied in three transsexual populations. In the Swedish population, they demonstrated that the length of the (TTTA)*n* repeat in the fourth intron of the CYP19 gene did not differ from the control group, when dichotomized in short (<7 and long ≥7 repeats) (Henningsson et al., 2005). This finding was confirmed in the Australian/American (Hare et al., 2009) and the Japanese (Ujike et al., 2009) populations. The length of the dinucleotide CA repeat in intron 5 of the ERβ gene was also demonstrated not to differ from the control population (Hare et al., 2009; Henningsson et al., 2005; Ujike et al., 2009).

In one study, the TA repeat promoter region of ERα was investigated, and it was shown that the distribution of repeat numbers was not significantly different in FtM and MtF, compared with control females and males, respectively. In the Japanese study six polymorphisms of PGR were also investigated with identical results (Ujike et al., 2009). When interactions between genes and the odds for transsexualism were studied, only the first (relatively) small study population could demonstrate some interaction between AR and CYP19 (Henningsson et al., 2005). However, this was not confirmed in the two other studies (Hare et al., 2009; Ujike et al., 2009).

Bentz et al. (2007) studied the SRD5A2 V89L SNP in 100 MtF and 47 FtM transsexuals using 755 men and 915 women as controls and found that carriage of the mutant SRD5A2 Val89Leu L allele is not significantly associated with FtM and MtF transsexualism. The SRD5A2 was refuted as candidate gene of transsexualism. Subsequently, 102 MtF and 49 FtM transsexuals were investigated for the CYP17A2T>C SNP prevalence. There was no statistically significant difference between MtF and male controls in CYP17A2T>C SNP distribution. In contrast, FtM transsexuals did not follow the gender-specific allele distribution of their female pairs; rather, they had an allele distribution equivalent to MtF transsexuals and male controls. Therefore, the CYP17 was postulated to be a candidate gene for FtM transsexualism (Bentz et al., 2008). However, to date no further investigations have been reported.

2.3.4 Evaluation of Past Genetic Studies in Transsexuals

The heritability studies discussed in Sect. 2.2 provided a base to search for candidate genes involved in the development of gender identity and gender dysphoria. Given the fact that, as outlined in Chap. 1, sex steroids contribute largely to the sex differentiation of the brain, at least in animal models, it seemed only natural to investigate genes that are involved in either sex steroid biosynthesis or action. The results of these studies were rather disappointing. Of the genes involved in biosynthesis (CYP17, CYP19, and SRD5A2), only CYP17 appeared to be associated with FtM transsexualism, with an allele distribution equivalent to MtF transsexuals and male controls (Bentz et al., 2008). Of the sex steroid receptors investigated (AR, ERα, ERβ, and PGR), only the repeat length of the polyglutamine stretch of the AR was associated with MtF transsexualism (Hare et al., 2009; Henningsson et al., 2005). This finding, confirmed in two studies, does appear to support the theory of virilization of the brain through androgens since length of the CAG repeat is inversely proportional to the transcriptional activity of the androgen receptor, i.e., the longer the repeat, the higher the insensitivity for androgens thus leading to hypovirilization of the brain. However, the polymorphism of CYP17 is associated with higher estradiol and progesterone levels and yet is associated with FtM transsexualism. Given the fact that the allele distribution did not correspond to female controls, this paradox could be explained by a more male-typical expression pattern during embryonic and fetal development. As seen in rodents, levels of hormones are important but so are their timing and windows of susceptibility.

Hitherto, no strong candidate gene has emerged for the development of gender dysphoria. Because of the complexity of gender identity development, it does not seem likely that one single gene will be discovered. Gender identity is such a robust and prominent trait that polymorphisms of genes alone are unlikely to account for the development of gender dysphoria. In addition, the genes investigated involved hormonal pathways, and, nowadays, more data have emerged of effects on sex differentiation that are not attributable to hormonal action but that arise from expression of X and Y genes within non-gonadal cells and result in sex differences in the functioning of those cells (Ngun et al., 2011). These effects may provide a different angle to pursue the genetic basis of gender identity and gender dysphoria. In the Sect. 2.4, these so-called sex chromosome effects are further addressed.

2.4 The Classic Theory Revisited: The Unified Model

The classical theory of brain and sexual behavior and the research based on its conceptual framework of organizational and activational effects of sex hormones on cells are extensively addressed in Chaps. 1 and 3. In this section we will go beyond organization and activation by discussing sex chromosome effects in humans and animals, exploring phenomena that do not adhere to the classical theory, with its focus on brain differentiation. Finally, we will present a new paradigm of sex differentiation that includes both the organizational–activational hypothesis and sex chromosome effects.

2.4.1 Sex Chromosome Effects

The male and female zygote, the cell formed by the union of a sperm cell and an egg cell, has an identical set of autosomes (nonsex chromosomes), which comprise about 95 % of the genome. Those common genetic factors make men and women very similar in their function. It is noteworthy that a recent meta-analysis of genome-wide-association studies comprising 114,863 individuals (61,094 women and 53,769 men) of European ancestry showed no autosomal differences between men and women (Boraska et al., 2012). The sex chromosomes, comprising the other 5 % of the genome, differ in three main ways in the zygote: (1) Only males have Y genes, (2) the two sexes differ in the copy number of X genes (although the sex-specific effect of this difference is largely eliminated by X inactivation), and (3) females receive a paternal X imprint that is lacking in the male. As the individual develops, however, other intrinsic genetic sex differences arise that are not caused by gonadal hormones. One X chromosome is randomly selected to be transcriptionally silenced in each female cell, and about half of the cells activate the maternal X chromosome and express the maternal X alleles or maternal imprint, and the other half express the paternal X alleles or imprint. Thus, female tissues are mosaic and might differ in phenotype from tissues that are not mosaic (male) (Arnold & Burgoyne, 2004; Migeon, 2007). In addition, X inactivation may make females more vulnerable than males to some genetic mutations or environmental perturbations at early stages of embryonic development, as was demonstrated in mouse models (Chen et al., 2008).

Patients with Turner syndrome have a basically female phenotype and were shown to have a 45X sex karyotype (Ford, Jones, Polani, De Almeida, & Briggs, 1959). In contrast, patients with Klinefelter syndrome have male genitalia, including testes, and are characterized by 47XXY (Jacobs & Strong, 1959). This appeared to confirm the concept of the male as the induced state, and the presence of a single Y seems to override the effects of even more than one X chromosome; even XXXXY individuals have testes (Hayek, Riccardi, Atkins, & Hendren, 1971). However, in Klinefelter syndrome (XXY) patients, as well as in XXXXY, the testes are very abnormal and the phenotype is partially feminized. The latter may include female bodily habitus and body-hair distribution, gynecomastia, and feminine pitch of the voice. The mechanism behind this feminization is not known, but it is presumed to be due to the presence of a significant level of estrogens, as the result of more than one active copy of an X chromosomal gene that directs the development of estrogen-producing cells. Likewise, in Turner syndrome (45X), the phenotype, though "basically" female, is in fact in fundamental ways different from 46XX females. For example, normal breast development may be lacking, and, most importantly, though ovaries with oogonia (egg cell precursors) are present in fetal stages, in adults the ovaries are absent and replaced by “streak gonads” (underdeveloped and fibrous dysfunctional tissue). This suggests that two copies of a non-inactivated X chromosomal factor are required for normal postnatal development of the ovary. Thus, the “default” situation of absence of Y does not produce normal ovaries in the absence of a second X, and normal female phenotype is not a default state caused by absence of Y but rather a status that requires the presence of two functional copies of at least one X chromosomal gene (Blecher & Erickson, 2007).

In humans, sex chromosomal abnormalities can illustrate how sex chromosomes play a role in the phenotypic differences typically seen between 46XY men and 46XX women: 46XX girls score better than boys on tests of social cognitive skills (Skuse et al., 1997). Adolescent girls with Turner syndrome are more likely to have social difficulties compared to 46XX girls (McCauley, Feuillan, Kushner, & Ross, 2001). Since both 46XY boys and 45X girls experience more social adjustment problems compared to 46XX girls, there may be a genetic locus involved in social cognitive skills on the X chromosome, and this locus may be subject to imprinting (the process in which one specific allele of a gene comes to expression when it is inherited from one specific parent, either the father or the mother). Significant differences have been reported between 45Xp Turner syndrome girls (in which the X was of paternal origin) and 45Xm girls (in which the X was maternally derived) in terms of social skills: 45Xp girls had superior social competence and social skills compared to 45Xm girls, suggesting that the genes in this locus are expressed only from the paternal X (Skuse et al., 1997). This could potentially be one of the reasons why boys are more susceptible to disorders such as autism that affect social adjustment and social skills such as language. In boys, the X is only of maternal origin, and therefore this locus would be silenced (Skuse, 2000).

In animals, the mouse model mostly used to study sex chromosome effects is the “four core genotype” (FCG) model: The testis-determining gene (*Sry*) was moved from the Y chromosome to an autosome (by deletion of *Sry* from the Y and subsequent insertion of an *Sry* transgene onto an autosome), so that testis development occurred independently of the sex chromosome complement (i.e., XX or XY). Results were that XX mice developed testes, while XY mice that lacked *Sry* developed ovaries. This allowed the comparison of mice with the same-sex chromosome complement (XX versus XX(+Sry) or XY and XY(−Sry)) but with the opposite gonadal phenotype (ovaries versus testes). Thus, if a trait varies by gonadal phenotype (XX(+Sry) and XY differ from XY(−Sry) and XX), it is considered hormonal in origin, and if it varies by chromosome complement [XX and XX(+Sry) differ from XY and XY(−Sry)], it is considered genetic in origin (De Vries et al., 2002). To date, the model demonstrated that for most of the investigated traits, there were no differences between XX and XY mice that had the same gonadal sex. Thus, the organizational–activational framework accounted completely for the majority of the classic sex differences first studied in the FCG model (McCarthy, Arnold, Ball, Blaustein, & De Vries, 2012). However, the model could also demonstrate a sex chromosomal basis for sex differences in both brain structures and behavior. The vasopressin fiber density in the lateral septum, part of the limbic system, was greater in XY mice with either testes or ovaries compared to XX mice with the same gonadal sex (De Vries et al., 2002; Gatewood et al., 2006). During embryogenesis, the increased susceptibility to neural tube defects in females is caused by XX versus XY differences in the genome and not by gonadal hormones (Chen et al., 2008). In addition, XY gonadal females were more aggressive than XX females. When tested for response to nociceptive stimuli (thermal and chemical), the XX mice showed greater or faster response than XY mice, irrespective of their gonadal sex (Arnold, 2009a).

The FCG model may have certain limitations. One is that the gonads may not be equal in XX and XY mice of the same gonadal sex and therefore secrete hormones differently during critical stages of development. However, it was found that XX and XY mice of the same gonadal sex do not differ in many traits that are responsive to the organizational effects of gonadal hormones, suggesting that these mice have similar hormonal levels. Also, the Sry transgene placed on an autosome (nonsex chromosome) may behave differently compared to the "regular" Sry gene. To address these limitations, mice were gonadectomized followed by an administration of equivalent doses of gonadal steroid hormones. In addition, it remains unclear when a sex difference is attributed to the complement of sex chromosomes within cells and what the underlying cause is. It may be caused by (a) gene or genes encoded on the Y chromosome; (b) higher dosage of X genes, particularly the ones that escape X inactivation in XX animals; or (c) the paternal imprint of the genes encoded on the X chromosome in XX animals, which changes the expression of these genes to exhibit a female-specific pattern (Ngun et al., 2011).

2.4.2 Genetic Aspects of Brain Sex Differentiation

Some sexual dimorphisms in the brain and other somatic tissues cannot be solely attributable to the effects of gonadal steroid hormones. For instance, the zebra finch male can sing a courtship song, whereas the female bird does not sing. This male-specific ability has been attributed to several brain regions that are much larger in the male. Based on the classical view, two pathways of development were conceptualized. Either the steroid hormones produced in the testes cause a masculine pattern of neural development or, alternatively, the steroid hormones secreted by the ovary cause female brain development and block masculinization, as was shown in other bird species for several male characteristics (Arnold, 1997). The initial studies indeed demonstrated that administration of estrogens or androgens to hatchling females caused masculine neural development (Gurney & Konishi, 1980). Androgens that cannot be converted to estrogens (dihydrotestosterone) caused less masculinization, and androgens that can be converted to estrogens (testosterone) were less potent than estradiol. Therefore, it was postulated that estradiol is the masculinizing agent in females. However, the masculinizing dosage of estrogen is very high and results in supraphysiological levels for both females and males. Therefore, it may be that the masculinizing actions of estrogen are pharmacologic and do not normally occur in males. Also, none of the steroid treatment regimens have led to the development of a completely masculine neural circuit. To test the second theory—a feminizing and demasculinizing effect of estrogens—hatchling males were treated with estrogen but not much effect on anatomical differentiation of the song circuit was observed (Schlinger & Arnold, 1991). Also, androgen deprivation by either castration (Arnold, 1975) or treatment with the androgen receptor blocker, flutamide (Schlinger & Arnold, 1991), could not prevent masculine differentiation. To test the putative role of estrogen as the main mediator, males were treated with an inhibitor of estrogen synthesis, fadrozole. This treatment also failed to cause any consistent demasculinization of neural development in genetic males. Likewise, when (genetic) female embryos with viable and secreting testicular tissue and absent ovarian tissue were created, their neural song system showed little or no masculinization. In conclusion, in the zebra finch, testicular steroid secretion is not solely responsible for the masculinization of the brain (Arnold, 2009b).

In mammals, mice without both adrenals and gonads were studied. These steroidogenic factor 1 knockout (SF-1KO) mice do not express steroidogenic factor 1 (SF-1, NR5A1), a member of a nuclear receptor superfamily of transcription factors which is normally expressed in steroidogenic as well as non-steroidogenic tissues. They are born without gonads and adrenal glands and have nonfunctional gonadotropic cells in the pituitary and an altered organization of the ventromedial hypothalamus (VMH). In SF-1 KO mice, gonadal ridges form normally on embryonic day 10.5 (E10.5) but undergo apoptosis immediately thereafter, and gonadal ridges disappear by day E12.5 (Ikeda, Shen, Ingraham, & Parker, 1994). Consequently, SF-1 KO mice develop female internal and external genitalia without gonads irrespective of genetic sex. Because expression of steroidogenic enzymes in mouse fetal gonads is present around day E13 in testes (fetal ovaries are hormonally inactive) coinciding with the start of testosterone production (Budefeld, Jezek, Rozman, & Majdic, 2009), SF-1 KO mice are not exposed to endogenous gonadal hormones. Therefore, they represent an excellent model to study gonad-dependent versus gonad-independent brain sexual differentiation in the absence of *SF-1* gene. SF-1 KO mice normally die shortly after birth due to adrenal insufficiency but can be rescued by corticosteroid treatment and adrenal transplantation. It was found that the expression of neuronal nitric oxide synthetase in the caudal preoptic area/anterior hypothalamus was enhanced in wild-type and SF-1 KO males and considered the result of gonad-independent sex differentiation. This was also found in the anteroventral periventricular preoptic area (AVPV). Therefore, some sex differences present in agonadal SF-1 KO mice likely arise due to different complements of sex chromosomes or disruption of a functional *SF-1* gene and not due to differential exposure to sex steroids during prenatal/early postnatal development (Budefeld, Grgurevic, Tobet, & Majdic, 2008).

One other approach to investigate sex differentiation of the brain is to interfere directly with sex chromosome gene expression. Early transcription of the Y chromosomal gene SRY can be detected in the human zygote in the one-cell stage (Ao, Erickson, Winston, & Handyside, 1994; Fiddler, Abdel-Rahman, Rappolee, & Pergament, 1995), and a faster rate of cell division has been reported in male embryos (Pergament, Fiddler, Cho, Johnson, & Holmgren, 1994). In mice, transcripts of Sry can be detected in the blastocyte stage (Zwingman, Erickson, Boyer, & Ao, 1993). In addition to the gonad, Sry is expressed in the embryonic murine brain, including the mesencephalon (midbrain) and the hypothalamus (Mayer, Mosler, Just, Pilgrim, & Reisert, 2000). Indeed, in the FCG mouse model, mesencephalic brain cells (neurons) were grown in cultures, and it was shown that cells of XY mice, irrespective of their gonadal sex, developed more dopaminergic neurons (Carruth, Reisert, & Arnold, 2002). This confirmed earlier studies in which rat embryonic mesencephalic cells in culture demonstrated sex differences in a developmental stage prior to sex steroid production (Reisert & Pilgrim, 1991). To explain this kind of differentiation, it was postulated that the expression of a gene on the Y chromosome in brain development would bias the development of neural circuits. Indeed, the expression of Sry was detected in both the human and mouse brain (Arnold, 1996). In the mouse brain, Sry messenger RNA is present through all developmental stages and in adulthood (Mayer et al., 2000). The translation of mRNA into the actual protein product can be inhibited with the so-called antisense oligodeoxynucleotides (ODN). Using this technique by infusing Sry antisense ODN in male rats, it was demonstrated that downregulation of Sry, specifically expressed in tyrosine hydroxylase-expressing neurons in the substantia nigra (SN), causes a significant decrease in tyrosine hydroxylase expression with no overall effect on neuronal numbers and that this decrease leads to motor deficits in male rats. This study was the first to report that Sry directly affects the biochemical properties of the dopaminergic neurons of the nigrostriatal system (Dewing et al., 2006). In addition, the effect of Sry antisense ODN in the SN on specific motor functions was assessed by the akinesia and limb-use asymmetry tests (Schallert, Fleming, Leasure, Tillerson, & Bland, 2000). In the akinesia test, animals with unilateral (one-sided) dopamine depletions take fewer steps with their forelimb opposite to the depletion side than they do with their forelimb at the same side of depletion. These results demonstrate a direct male-specific effect on the brain by a gene encoded only in the male genome, without any mediation by gonadal hormone (Dewing et al., 2006).

2.4.3 A New Paradigm on the Origins of Sex Differences in All Tissues

The classical paradigm of human and mammalian sexual development states that the genetic factors that determine sex only influence the fate of the gonad. A maleness factor produces testes (primary sex determination). These organs secrete hormones which cause male secondary sexual differentiation. In the absence of the maleness factor, by default the gonad becomes an ovary, and the absence of testicular hormones leads to female secondary differentiation. Building on this foundation, a new model which addresses both the classical organizational and activational effects and the more recently discovered sex chromosomes effects was proposed by Arnold in 2009 (Arnold, 2009b):

> All ontogenetic sex differences in phenotype derive from the differences in the effects of sex chromosome genes, which are the only factors that differ, on average, in the male and female zygote. A subset of X and Y genes represent the primary sex-specific factors causing sex differences in development and adult phenotype. Primary among these is Sry because it controls sexual differentiation of the gonads, and therefore sets up life-long sex differences in secretion of gonadal hormones. These hormones, especially testosterone and estradiol, act throughout the body in an organizational (long-lasting or permanent) and an activational (reversible) fashion at different times of life, to cause most known sex differences in phenotype, including sex differences in susceptibility to and progression of diseases. In addition to Sry, however, various X and Y genes have differential effects on male and female cells because of the constitutive sex differences in the copy number and/or parental imprint on these genes. Various sex-specific factors interact, acting synergistically or counteracting each other or otherwise conditioning the effects of each other. Thus, XX and XY cells are different prior to the secretion of gonadal hormones, and gonadal hormones affect XX and XY cells unequally.

The key in this model is that the previous emphasis on the action of gonadal hormones on non-gonadal tissue as the sole agent to cause sex differences is now shifted away towards primary sex-specific effects of X and Y genes. However, gonadal hormonal action does remain the most important among a variety of secondary factors downstream of the sex chromosomes. And thus doing so, the X and Y genes are given primacy, based on the fact that these are the only factors in the zygote that ultimately result in sex difference in phenotype. On the genetic level, three factors are considered to be determinates of sex differentiation: (1) Sry, (2) other putative Y and X genes, and (3) the constitutive difference in XX and XY genomes (as discussed in Sect. 2.2). The gonadal steroidal secretion still remains a major factor among the secondary proximate factors (those not sexually dimorphic in the zygote) because of its widespread and dominant effect on sexual phenotype. This proposed model is unified because it applies equally to all tissues and sex differences in phenotype. Previously, the sex differentiation of the gonads was seen as genetic and therefore classified as sex determination, and the sex differentiation of other non-gonadal tissues was considered to be caused by hormonal action. This implied a separation of gonads and other tissue, which has now disappeared. The reunification of gonads and other tissues provides an attractive concept but raises the question of how to integrate future investigations of direct genetic and hormonal factors and their interaction (Arnold, 2009b).

2.5 Conclusions and Future Perspectives

The results thus far show that heritability studies demonstrate that genetic components play a role in the causation of gender dysphoria. Second, it is unclear whether genetic variations (polymorphisms and mutations) that involved in sex hormone production or activity (including receptors) and that predispose for disorders of sex development also predispose for gender dysphoria. Most of the genetic studies measuring one or more of these variants show no clear difference between subjects with gender dysphoria (i.e., most often patients referred for sex reassignment treatment) and control subjects. On the other hand, several studies show an increased prevalence of gender dysphoria in subjects with disorders of sex development (De Vries, Doreleijers, & Cohen-Kettenis, 2007). However, it is not clear whether this is the result of the underlying genetic disorder or associated with a more complicated psychosocial development.

Future studies on the genetic causes of gender dysphoria could develop along two lines of research. One way is to study the genetic causes of sex differences in the brain, supposing that gender dysphoria may be a result of deviations in the sexual differentiation of the brain. Under this assumption, future studies will require incorporating classic endocrine methods to manipulate hormone synthesis and action, modern molecular genetic methods to alter hormone action in a cell-type-specific manner, as well as methods to manipulate the copy number and expression of X and Y genes that underlie constitutive genetic differences in XX and XY cells. When investigating sexual differentiation, one should expand one's conceptual horizons beyond an appreciation for how gonadal hormones cause sex differences to include an understanding of the sex chromosomes and the direct effects of genes encoded on these chromosomes and the interaction of these genes with the rest of the genome (Arnold, 2009b). In this respect, the emerging field of epigenetics may provide promising opportunities.

Cells of a multicellular organism are genetically homogeneous but structurally and functionally heterogeneous, owing to the differential expression of genes. Many of these differences in gene expression arise during development, including sex differentiation, and are subsequently retained through cell division. Epigenetics refers to the study of stable alterations in gene expression potential that arise during (1) development, (2) differentiation, and (3) under the influence of the environment. In addition, epigenetic regulation of gene expression allows the integration of intrinsic and environmental signals in the genome, thus facilitating the adaptation of an organism to its changing environment through alterations in gene activity (Jaenisch & Bird, 2003). The epigenome refers to the ensemble of coordinated epigenetic marks that control the accessibility of the DNA to the machinery-driving gene expression. The best understood epigenetic marks are modifications of core histones, proteins that package DNA, and methylation of DNA itself (addition of a methyl group to the cytosine side chain in cytosine–guanine (CpG) dinucleotides) (Reik, 2007). In the context of sex differentiation, epigenetic changes offer a plausible mechanism by which early hormonal effects could be hardwired into the genome to channel adult hormonal and behavioral responses. In rodent models, steroid receptors are subjected to epigenetic programming. DNA methylation of ERα increases across development of the cortex in both sexes, concomitant with reduced gene expression. Furthermore, males exhibit more ERα promoter DNA methylation and reduced expression compared with females in certain regions. For the AR it was shown that methylation of its core promoter was increased by testosterone and decreased by estradiol. Epigenetic mechanisms mediate between the sex and the genetic blueprint. The expression potential of estrogen receptors, androgen receptors, and progesterone receptors can be sex- and tissue-specific fine-tuned by epigenetic mechanisms. The transcriptional activities of these genes depend on the recruitment of the epigenetic machinery and modification of epigenetic marks governing gene expression. This process is dynamically regulated during brain development and shows a sex-dimorphic expression in distinct tissues and is under influence of sex steroid action. Moreover, the epigenetic machinery itself can show sex-specific differences in the expression and activity of single components in distinct tissues. Together, the mutual interplay between these regulatory layers critically determines how hormonal signals are sex-specifically translated into sustained changes of neuronal substrates during sexual development and differentiation (Menger et al., 2010). Studying the epigenome in transsexuals may help in identifying genes involved in gender identity development and also gain more insight in sex-steroid-mediated events in brain sex differentiation. Since the epigenome is also responsive to the environment, epigenetics may also provide a biological substrate for identifying psychological and social factors in gender identity development. It was shown in rats that differences in maternal grooming of male pups resulted in a sex-specific DNA methylation pattern of the ERα promoter. Simulation of this type of grooming in female pups resulted in a male-specific DNA methylation pattern of the ERα promoter (Kurian, Olesen, & Auger, 2010). These studies illustrate how early social experiences implement sex differences via epigenetic programming. Next to sex-steroid-related genes, sex chromosomes are also subjected to epigenetic programming. The X inactivation and possible imprinting of genes on the X chromosome that escape inactivation, as discussed in Sect. 2.4.1, are due to epigenetic mechanisms. In this perspective, the finding that MtF transsexuals have a significant excess of maternal aunts versus uncles prompted the hypothesis that MtF transsexuals may inherit feminizing X chromosomal imprinted genes. The underlying mechanism was postulated to be a failure to erase the imprint on the paternal X chromosome in the egg cell of the grandmother, followed by a second passage through the mother (Green & Keverne, 2000). Although the biological evidence, i.e., epigenome, is lacking, it does offer a new perspective to investigate sex chromosome effects in brain sex differentiation.

A second line is to apply genome-wide studies (including single-nucleotide polymorphisms, copy number variation, and also degrees of methylation) on subjects diagnosed with gender dysphoria. Such genome-wide studies have the advantage to have no prior hypothesis about which genes are involved, but in general these studies require a large number of participants. Important questions include whether genes predisposing for gender dysphoria are the same for male-to-female as for female-to-male transgendered persons. Second, in order to solve the power problem in this approach, the question arises as to which part of the genome is most likely to be associated with gender dysphoria. Given the above-mentioned literature, it is recommended to start with the study of the sex chromosomes.

Finally, the combination of magnetic resonance imaging (MRI) data and genome-wide arrays provides another option to study the genetic variation that underlies the phenotypic variation in those areas of the brain that are different in men and women.

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Chapter 3
Gender Identity Development: A Biopsychosocial Perspective

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Abstract From the first time individuals described a felt incongruence between their assigned and their experienced gender, people have been interested in the origins of gender dysphoria and transsexualism. This chapter focuses on the various theories and research evidence about gender identity development, which have often pointed to a biological, a psychological, or a social factor as determining one's gender identity. Over time, differing views prevailed, although the multiple perspectives also developed parallel to one another. Two distinct lines of research on gender identity development emerged: those focused on "normative" development and those focused on nonnormative or gender-variant development. The chapter first describes the multiple factors (biological, psychological, and social) that were studied in both lines of research. After that, current studies are presented that give evidence for a complex interaction of biological, psychological, and social factors in gender identity development. Recent findings from neuroimaging and genetic studies of individuals with gender dysphoria provide evidence that nature is of importance. Its exact role however remains largely enigmatic.

Regarding future studies of gender identity development, we conclude that they should seek to understand not only the potential genetic and environmental (from both nature and nurture) factors, but also when these factors emerge in life and how

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those factors may be of influence on the full spectrum from gender-normative to gender-variant development in all its expressions.

3.1 Introduction: The Past, the Present, and the Future

Over the last century, theories and views about gender identity development have been formulated and changed substantially. The focus of theorizing and empirical studies has been to examine which factors determined *gender identity* (one's identification as male, female, or another gender), the malleability of gender identity, and the age at which gender identity was established. Another important concept in the study of gendered behavior and identity includes *gender role*: behaviors, attitudes, and personality traits that are typically attributed to, expected from, or preferred in a boy or a girl. Gender role behavior, masculine or feminine behavior, can to a certain extent also be studied in animals, whereas gender identity involves the labeling of a person's sense of self and, as a typically human characteristic, obviously cannot be studied in animals. Two distinct lines of research have emerged with a focus on gender identity: those focused on "normative" development and those focused on specific subpopulations such as individuals with gender dysphoria (discomfort with the assigned gender identity) or those who have a disorder of sex development (DSD). Studies of "gender variance," gender role behaviors, interests, and preferences that may be nonconforming to traditional gender roles but may not be associated with desires for sex reassignment, have typically been incorporated into studies of normative development. For example, studies of gender and self-concept in masculine or feminine domains such as math or computers stem from the normative literature (Sáinz & Eccles, 2012), but illuminate concepts associated with gender nonconformity that can inform the study of gender variance.

We are beginning to see a convergence of these lines of research such that inquiry should ultimately identify factors associated with variability of gender identity (studied via the mechanisms of gender variance and gender role behaviors) across the entire spectrum. In this chapter, we examine theoretical concepts and research findings, as well as incorporate terminology from both lines of research. We conclude with proposed concepts and strategies to move the field forward in developing an integrative theoretical framework to better understand variability in gender identity development.

In this chapter, we will use the biopsychosocial perspective of gender identity development. It was Engel (1977) who introduced the "biopsychosocial" model as an alternative to the pure "medical model" that was used in medicine at that time. He felt that Western society had adopted the medical model not only as a scientific model to study the origins of disease but also as a cultural belief system. In his view, the biomedical model is used as an explanatory system for "natural phenomena that are puzzling and disturbing," and it provides "a device for social adaptation." The reductionist biomedical model viewed the body as a machine in which disease simply meant a breakdown that had to be repaired. The more holistic biopsychosocial approach, however, would incorporate behavioral and psychosocial aspects of health. It would give a more thorough understanding and a fuller acknowledgement of all factors that play a role in health and diseases (Engel, 1977).

Some might consider the biopsychosocial perspective "outdated," as it dates back to the last decades of the former century. However, when reflecting on gender identity and gender dysphoria, we feel that this model still helps us to fully appreciate the different factors that influence gender identity development. Gender identity touches upon a sensitive part of everybody's personality. The extent to which gender identity is determined by biological versus social or psychological factors raises strong emotions in many people, especially those who work with or are affected by gender dysphoria.

Historically, the various authors that conceptualized their theories on gender identity development often adopted a biological, a psychological, or a social view. Certain views prevailed at different times, although the perspectives also developed parallel to each other. Currently, contributions from each of these perspectives allow for a richer understanding of the complex ways in which gender identity develops across a broad spectrum. Attempts to understand gender identity development will likely ultimately require a nuanced understanding of the ways in which biological, psychological, and social factors interact with one another.

Before the 1950s, Freud's personality development theory prevailed, positing that variability in gender identity was due to anomalous, early childhood psychosexual experiences, specifically during the phallic stage between ages 3 and 6 (Freud, 1962). A shift in thinking occurred in the 1950s when Money proposed the idea that core gender identity was malleable and could be formed by raising a child as male or female during a critical period in early childhood (Money, Hampson, & Hampson, 1955). Although Money's perspective has been shown to be wrong, the role of social factors in gender identity development has been of interest to many scholars, and there is evidence of its importance.

In the 1960s, Kohlberg formulated a cognitive theory of gender identity development, proposing that children develop gender identity after they are cognitively able to understand that gender differences exist and understand the lifelong consequences of gender identity (Kohlberg, 1966). Cognitive psychology further influenced theorizing about gender identity by introducing the "gender schema theory" in the early 1980s, which argued that, while growing up, children develop a "gender schema," a network of gender-related information coloring and influencing their behaviors (e.g., Bem, 1981).

Various theories have incorporated the importance of social factors for gender identity development. Early social learning theory emphasized gender role behavior and how it is shaped by reward (of gender-appropriate play). In the 1970s and 1980s, psychosocial theories argued that sex-segregated peer networks reinforced stereotypical gender behaviors (e.g., Maccoby & Jacklin, 1987). Bandura argued for the importance of gender role modeling (Bussey & Bandura, 1999).

However, these theories did not seem to work for atypical gender development. How can one explain a felt incongruence between gender identity and sex of birth?

During the 1990s, the attention shifted again, this time to the role of biological factors in gender differences and also in gender identity development. Modern brain studies not only revealed that there are structural differences between males and females in size and distribution of white and gray matter, but that these differences are correlated with differences in cognitive functioning (e.g., Gur et al., 1999). With regard to gender identity, a specific brain area was identified in transsexuals that was similar in size to that of the identified sex instead of the assigned biological sex (Zhou, Hofman, Gooren, & Swaab, 1995). These studies led to high expectations of what biological factors might clarify in regard to the behavioral differences between males and females.

Until recently, most knowledge about gender development came from studies in general population samples. For a long time, the focus has been on normative gender development, which typically makes no distinction between gender development and gender *identity* development, the latter being of utmost relevance for gender-variant development. In this chapter, we are interested in gender *identity* development, although it is important to realize that most studies of normative gender development focus more on gender differences in overt gender role behaviors, such as toy preferences, than on gender *identity* development.

3.2 Normative or Typical Gender Identity Development

Boys and girls grow up differently. As soon as they are born, behavioral differences can be observed. When newborns, quietly lying in their mothers' laps, are confronted with a friendly face and a mobile made of the same colors and sizes as the face; girls spend more time looking at the face whereas boys take more time looking at the physical-mechanical object (Connellan, Baron-Cohen, Wheelwright, Batki, & Ahluwalia, 2000). As infancy progresses, additional gender differences have been observed. Six-month-old boys have greater difficulty than girls in maintaining affective regulation (they are, e.g., more likely than girls to fuss, to gesture to be picked up, and to try to escape or get away by turning and twisting) (Weinberg, Tronick, Cohn, & Olson, 1999). Sex-typed toy preferences exist as early as age 12–24 months (Jadva, Hines, & Golombok, 2010), with boys showing more interest in a car compared to a doll and vice versa. Interestingly, it was not the color or the shape of the toy that mediated the preference; for example, girls preferred a blue doll over a pink car. In general, both boys and girls preferred reddish colors over blue and rounded over angular shapes (Jadva et al., 2010). So at this young age, no color preferences were found, yet in older children, girls tend to prefer stereotypically feminine colors (pink/purple and warm colors), and boys generally choose the masculine colors (blue, brown, and darker colors).

During the preschool years, more behavioral gender differences emerge. Five-year-old girls are better able to give socially desirable solutions for stories of children with a conflict, like proposing to play together or get a teacher or a parent to mediate. Boys more frequently come up with verbally or physically aggressive solutions (Walker, Irving, & Berthelsen, 2002). In primary school, most children have begun to control their emotions and physical aggressiveness is displayed less frequently. However, boys still show more verbal and behavioral negativity than girls when they are observed while losing a computer game (Underwood, Hurley, Johanson, & Mosley, 1999). For the individual boy or girl, one should be cognizant of the fact that these observed behavioral gender differences show large overlap, and the variability within the sexes is often greater than between sexes.

Variability in sex-typed behavior exists from a young age. Masculine girls and feminine boys can be recognized, as well as feminine girls and masculine boys. Interestingly, the degree of sex-typed behavior observed as a toddler predicts the degree of sex-typed behavior in adolescence (Golombok, Rust, Zervoulis, Golding, & Hines, 2012), suggesting that degree of sex-typed behavior may be very consistent over time. Also, between late childhood (11 years of age) and early adolescence (15 years of age), sex-typed behaviors increase, and again, sex-typed behavior at age 11 predicts individual differences 2 years later (McHale, Shanahan, Updegraff, Crouter, & Booth, 2004).

Hill and Lynch (1983) proposed that in adolescence, *gender intensification* occurs. This means that an increased pressure to conform to culturally sanctioned gender roles results in a further differentiation in gender role identification in boys and girls. Studies testing this idea have shown mixed results. For example, Galambos, Almeida, and Petersen (1990) indicated that sex differences in masculine personality qualities (instrumental qualities such as independence and leadership) increased in early adolescence, but sex differences in feminine personality qualities (expressive qualities such as sensitivity and kindness) did not. A longitudinal study by Priess, Lindberg, and Hyde (2009) showed that adolescents did not become more stereotypical in their gender role identity across adolescence. The authors attributed the lack of support for the gender intensification hypothesis to changed patterns of socialization in present-day adolescents. In present-day society, boys are free to be expressive and girls are supported in being more independent than they were in the past.

The affective component of gender identity (gender contentedness) is also an important factor during development influencing well-being. Feeling gender typical and content with one's gender generally positively influences well-being, whereas feeling pressure to conform to gender stereotypes is generally a negative influence (Carver, Yunger, & Perry, 2003). Developmentally, older children seem to feel more gender typical compared to younger children, while at the same time, they experience less pressure to conform to the gender stereotypes (Carver et al., 2003).

3.2.1 Biological Factors

In a key paper by Phoenix, Goy, Gerall, and Young (1959), effects from sex hormones during prenatal development on the differentiation of the brain towards a male or female direction were first called organizing effects. Since then, numerous animal studies have revealed that sex hormones, testosterone in particular, not only guide the development of the genitals but also affect sexual differentiation of the brain and behavior (McCarthy, De Vries, & Forger, 2009; see also Chap. 1). In humans, the effects of prenatal sex hormones are more difficult to study, but it is not unlikely that sex hormones influence the development of gender role behaviors, as well as gender identity (the conviction of being a man or a woman) (Hines, 2009; Steensma, Kreukels, De Vries, & Cohen-Kettenis, in press). In this section, we consider the studies examining biological links to gender identity development in humans. Later, we focus specifically on studies examining biological factors in gender-variant populations. For studies of the prenatal effects of sex hormones on gender development, it is important to make a distinction between gender role behavior and gender identity.

The case of an identical twin from Winnipeg was one of the first to show that biological factors in gender identity development could not be ruled out (Diamond & Sigmundson, 1997). This same-sex twin was raised as an opposite-sex twin after a disastrous accident, in which one of them lost his penis during circumcision. After consultation with John Money, the parents decided to raise their boy as a girl and not to mention to the twin what had happened. Although Dr. Money initially claimed otherwise, the boy raised as a girl was very unhappy in this assigned role. Studying the specifics of this case, we would say he/she was certainly gender dysphoric (i.e., the experienced gender identity was discordant from the assigned role). Immediately after the child was told the truth, he decided to reassume the male role. This boy who had a normal masculine prenatal development could obviously not be *turned* into a girl, so his gender identity was not as malleable as John Money had thought. Although this case strongly indicated that biological factors do matter in gender identity development, they do not appear to be the sole factor. There are cases of people with ablatio penis who were raised as girls combined with early childhood gonadectomies, who do not appear to have gender dysphoria in the assigned role (Meyer-Bahlburg, 2005).

3.2.2 Psychological Factors

In their first year, infants as young as 3 or 4 months of age are capable of distinguishing between male and female faces (Quinn, Yahr, Kuhn, Slater, & Pascalils, 2002). Most research of these phenomena is done by habituation or preferential looking approaches. In a habituation approach, infants lose their attention when looking repeatedly to one of two categories, women or men. When the other category is presented, they show attention again. Earlier research indicated an ability to distinguish categories (sexes) in 75 % of infants at 12 months, 50 % at 9 months, and 35 % at 5 months (Fagot & Leinbach, 1993).

Whether children this young are able to categorize or *label* gender is still a matter of debate, however. Reaching the cognitive ability to label their own and others' gender is the first stage of what Kohlberg (1966) defined as *gender constancy*, the proposed notion that children must understand that they will always stay the same sex and that identification should be based on genitals. Gender constancy was proposed to develop in three stages between the ages of two and seven, although some studies suggest these stages are reached earlier (Slaby & Frey, 1975). These three proposed stages include *gender labeling*, the ability to label one's own and others' gender; *gender stability*, the recognition that gender does not change over time; and *gender consistency*, the recognition that gender does not change if someone's appearance or activities change but is generally ascribed to one's genitalia (for a review, see Ruble, Martin, & Berenbaum, 2006). Along with reaching the stage of gender constancy, most children develop a core sense of self as male or female and a gender identity congruent with their natal sex.

Holding these cognitive perceptions has consequences. Knowing basic gender information is related to increased play with the two most strongly stereotyped toys (trucks and dolls) (e.g., Zosuls et al., 2009). When toddler girls who responded to a test for gender labeling consistent with societal gender norms were compared to girls who responded inconsistently with gender norms, the former group showed less aggressive behavior than the latter. For boys this was not the case, suggesting that their overt aggression does not violate society's expectations for males (Fagot & Leinbach, 1985). Children also consciously choose which toy to play with. Girls who were told that a toy was typically female chose to play with it more frequently than when the same toy was presented to be typically male (Martin, Wood, & Little, 1990).

In a study asking 2–7-year-olds gender constancy questions, children gave more gender constant answers when they were older (Levy, 1998). When asked to attribute gender-specific activities to pictures of either a boy or a girl engaged in different behaviors, building blocks, playing a ball, and using a tool were considered masculine, while taking care of a baby, playing a doll house, and doing makeup were considered feminine. Children thus construct cognitive gender schemas during development; these are organized networks of mental associations representing information about themselves and the sexes that influence information processing and behavior (for a review, see Martin, Ruble, & Szkrybalo, 2002). Before children reach gender constancy, most have acquired knowledge about gender stereotypes (girls have long hair and boys short hair) and gender-stereotyped behavior (boys are aggressive, girls take care of others). Most children have an active role in their gender schema development as they, for example, remember gender-consistent information better than gender-inconsistent information. In their thinking about sex-typed traits and behavior, young children are fairly rigid; only after age 7 do they become more flexible (Signorella, Bigler, & Liben, 1993).

3.2.3 Social Factors

Social roles and expectations vary for girls and boys. Even before birth, gendered characteristics are ascribed to expected infants (Montgomery, 2010). For example, pregnant women experiencing much fetal movement may expect that their baby will be a boy. In the study of infants' behavioral gender differences (boys having greater difficulty than girls in maintaining affective regulation), mothers used different parenting strategies for boys versus girls. However, these differences were insufficient to account for the gender differences in infants' behavior (Weinberg et al., 1999). Another study described more favorable ratings of less nasal (male) vocalizations, even when the sex of the infant was unknown, suggesting both differences in sex and differential adult responses to sex differences (Bloom, Moore-Shoenmakers, & Masataka, 1999). The extent to which socialization factors contribute to the development of gender identity is not fully understood.

Social cognitive psychology emphasizes the role of environment in gender development: Modeling is one of the most pervasive means of transmitting values, attitudes, and patterns of thought and behavior, and children tend to choose, attend to, and associate with same-gender models (Bussey & Bandura, 1999). Evidence suggests that boys tend to do this more so than girls, for whom gender-atypical behavior is accepted more easily. As gender-stereotyped activities and interests are observed before children reach complete gender constancy, it is argued that modeling influences are important even in children's early gender development (Bussey & Bandura, 1999).

The most important consequence of a child's developing gender schema is probably that children increasingly choose to play with same-gender playmates. In the years between preschool and puberty, children consistently report spending more time with same-sex peers and siblings (Maccoby, 1998). Although many gender differences are quite small, gender accounts for a very large proportion of the variance in children's play partners (Maccoby, 1998). Children thus spend a major part of their time in all-male or all-female groups and grow up in different subcultures. Consequently, gender segregation influences children's social development and friendships. Boys tend to play in larger groups and show more physical and rough and tumble play, and their social interaction is more dominance related. Girls play in less hierarchically organized groups and show more close friendships.

In their thinking about sex-typed traits and behavior, the gendered context of one's family may influence gender attitudes. Although most youth report declines in stereotypical gender beliefs, firstborn boys with both brothers and traditional parents become more traditional across middle childhood and adolescence (Crouter, Whiteman, McHale, & Osgood, 2007). Children growing up in less traditional families, on the contrary, show more nontraditional gender role attitudes. For example, children growing up in Dutch lesbian families showed less traditional gender stereotypical thinking compared to children in heterosexual families (Bos & Sandfort, 2010). Cultural differences play a role as well. Italian children, for example, were more likely to favor stereotypical toys and activities than were Dutch children (Zammuner, 1987).

3.3 Gender-Variant Development

At the same time as gender-typical behavior emerges, some children will show what is also called gender-atypical or gender-variant development in early toddlerhood. These preschool children are boys displaying female interests and behavior and girls who strongly prefer male toys and playmates. They may even express an explicit desire to be the other gender as soon as they can talk (Cohen-Kettenis, 2005; Cohen-Kettenis & Pfäfflin, 2003). A recent long-term follow-up study found that gender-dysphoric children who insist they "are" the other gender are more likely to seek gender reassignment during adolescence than other gender-dysphoric children who state they "want to be" the other gender (Steensma, McGuire, Kreukels, Beekman, & Cohen-Kettenis, 2013).

Studies using the Child Behavior Checklist (CBCL), a parent-report behavioral problem questionnaire, show that cross-gender behavior in children is more common than the stated wish to be of the other gender (Achenbach & Rescorla, 2001; Cohen-Kettenis & Pfäfflin, 2003; Verhulst, Van der Ende, & Koot, 1996; Zucker & Bradley, 1995). For example, in a large Dutch twin study, 3.4 % of the 7-year-old boys and 5.2 % of the 7-year-old girls were reported to behave sometimes or often like the opposite gender, while only 1.0 % and 1.7 %, respectively, had stated the wish to be of the opposite gender (Van Beijsterveldt, Hudziak, & Boomsma, 2006). At age 10, these percentages had decreased, although less so for the stated wish. This shows that for many, cross-gender behavior diminishes when children reach their teenage years.

Presumably, only a small percentage of these children with gender-variant behavior fulfill the criteria for the diagnosis of gender identity disorder (GID). Although prevalence rates of GID in childhood are lacking, prevalence estimates in adults (male-to-female (MtF) transsexuals 1:10,000, female-to-male (FtM) transsexuals 1:30,000) indicate that this will probably be low (Zucker & Lawrence, 2009). The extent of gender-variant behavior and associated distress sufficient to qualify for a psychiatric disorder is a matter of serious debate, especially reconsidering the GID criteria for the upcoming DSM-5 and ICD-11 (Cohen-Kettenis & Pfafflin, 2010; Meyer-Bahlburg, 2010; Zucker, 2010). One important reason for this debate is that only a minority of GD children will be future gender reassignment candidates. Their gender-variant behavior may be pathologized considering that prospective studies of boys and girls with GD show that, at follow-up, the proportion of participants with a same-sex or bisexual sexual orientation is substantially higher than the base rates in the general population (Drummond, Bradley, Peterson-Badali, & Zucker, 2008; Green, 1985; Wallien & Cohen-Kettenis, 2008; Zucker & Bradley, 1995). In one unique longitudinal general population study of 879 Dutch boys and girls, gender-variant behavior was measured during childhood with the CBCL, while sexual orientation was assessed 24 years later, when participants were 27–36 years of age. The prevalence rates of same-sex orientation were, depending on the sexual orientation domain, 8.4–15.8 times higher in the childhood gender-variant subgroup, as compared to the childhood non-gender-variant subgroup (Steensma, Van der Ende, Verhulst, & Cohen-Kettenis, 2012). No one of the gender-variant subgroup in the general population was transsexual in adulthood, indicating that gender-variant behavior in childhood is indeed more predictive of same-sex sexual orientation in adulthood than later GD.

3.3.1 *Biological Factors*

Two lines of research are of particular interest to study the effects of sex hormones on gender identity development among gender-variant populations. First, by studying gender identity outcome in individuals whose sexual differentiation followed an atypical route, studies that have examined individuals with disorders of sex development (DSD). DSD are congenital conditions in which the development of chromosomal, gonadal, or anatomical sex is atypical (Hughes, Houk, Ahmed, & Lee, 2006). Second, studies that have examined sex-typical brain and behavior in individuals with a gender identity that is not in line with their assigned sex at birth.

3.3.1.1 Disorders of Sex Development

In individuals with DSD, both gender role behavior and gender identity have been studied. Many studies have found evidence for a role of prenatal testosterone in later masculine behavior (Hines, 2009). However, because the focus of this chapter is on gender identity development, we will confine ourselves here to studies focused on gender identity.

A recent study into psychosexual outcome in adolescents with various DSD found no signs for gender dysphoria or uncertainty about their gender identity (Jürgensen et al., 2012). Earlier studies did, however, report gender identity problems in certain DSD.

Congenital adrenal hyperplasia is an enzyme deficiency that exposes female fetuses to elevated testosterone levels. In general, women with CAH develop a female gender identity, but gender dysphoria occurs more often in this group than in women without CAH (De Vries, Doreleijers, & Cohen-Kettenis, 2007; Dessens, Slijper, & Drop, 2005). According to Jordan-Young (2012), the higher prevalence of masculine gender identity in women with CAH could arise from a slightly more masculine appearance caused by the physiological effects of CAH. The prevalence of gender identity problems did not, however, appear to be associated with the severity of genital masculinization, which can be seen as an indicator of the degree of prenatal androgenization (Dessens et al., 2005).

Children with 46 chromosomes and XY sex chromosomes (46, XY) who have 5α-reductase-2 deficiency (5α-RD-2) or 17β-hydroxysteroid dehydrogenase-3 deficiency (17 β-HSD-3) are usually born with female-appearing or ambiguous genitalia due to androgen biosynthesis problems. They are generally raised as girls, but at puberty when their genitals start to masculinize, transitions to the male role are not uncommon (De Vries et al., 2007). Children with 5α-RD-2 whose gonads are removed before puberty are more likely to maintain a female gender identity (Hines, 2009). The rise in testosterone levels after puberty therefore seems to be an important factor in gender identity formation and consolidation in individuals with this condition (Steensma et al., in press). We must, however, also consider cultural factors, because "gender role change occurs at different rates in different societies" (Hughes et al., 2006, p. 155).

Complete androgen insensitivity (CAIS) is a condition in which 46, XY individuals have testes and produce androgens but are insensitive to these androgens, causing their external genitals to develop in the female direction. Because of their complete female appearance, the diagnosis is often missed at birth and they are thus generally raised as girls and assigned to the female sex. Usually these women have a female gender identity and do not show signs of gender dysphoria (De Vries et al., 2007). Their brains could be hypothesized to have developed in the female direction because of the complete absence of androgen effects. But we should not forget that their physical appearance is also entirely feminine and they are nurtured in the female role. The combination of all these factors might have been necessary to develop a solid female gender identity in these individuals. However, T'Sjoen et al. (2011) have recently reported a female-to-male gender transition in a case with CAIS. Gender dysphoria and gender transitions occur more often in individuals with partial androgen insensitivity syndrome (PAIS) (Mazur, 2005). Regardless of the sex in which they are reared, around 25 % of individuals with PAIS seem to develop gender dysphoria (Warne, 2008). The partial susceptibility of their brains to the effects of prenatal androgens may have led to this more varied representation of gender identity and dysphoria (Steensma et al., in press).

Together, studies in individuals with DSD show that prenatal testosterone exposure of the brain may affect a male gender identity development. However, exposure to high levels of testosterone does not always lead to a male gender identity (e.g., in CAH). Therefore, it is still unclear from these studies how and to what extent prenatal androgens affect gender identity development. It is also not known how prenatal androgens interact with other factors to influence gender identity. In a letter to the editor, Cadet (a woman with AIS) nicely describes the deliberate evaluation of gender identity in a person with DSD (Cadet, 2011; Meyer-Bahlburg, 2011). It is not unlikely that the cognitive processes behind gender identity development in persons with DSD are rather different from those of non-DSD individuals.

3.3.1.2 Gender Dysphoria

Several postmortem studies have found that the brains of MtF transsexuals have some sex-specific characteristics that are more similar to females than males. In postmortem brain material of MtF transsexuals, the central portion of the bed nucleus of the stria terminalis (BSTc) and the interstitial nucleus of the anterior hypothalamus 3 (INAH3), sex-dimorphic nuclei in the human hypothalamus, appear to be similar in volume and number of neurons to that of women and smaller compared to that of men (Garcia-Falgueras & Swaab, 2008; Kruijver et al., 2000; Zhou et al., 1995). A more recent study of the same group shows that the volume and neuron number of another hypothalamic nucleus, the intermediate nucleus, of MtF transsexuals have intermediate values compared to those of men and women (Garcia-Falgueras, Ligtenberg, Kruijver, & Swaab, 2011).

Transsexuals thus show similarities in these nuclei with their experienced gender identity and differ from their sex of birth. The INAH3 is, however, also associated with sexual orientation and smaller in homosexual than in heterosexual men (Levay, 1991). For the BSTc, volume and neuron number in MtF transsexuals have been found to be smaller compared to both hetero- and homosexual men (Kruijver et al., 2000; Zhou et al., 1995). These findings show that, at least, these sex-dimorphic nuclei have developed in the direction of the experienced gender rather than in line with the birth sex. The extent to which these nuclei play a role in gender identity development remains to be determined.

One should keep in mind that these postmortem studies were all conducted by the same group in rather small samples. We are not aware of attempts to replicate these findings. And although the authors examined possible factors that might have influenced the results (by including material from castrated men, pre- and post-menopausal women, and MtF transsexuals that stopped taking cross-sex hormones before death), the influence of cross-sex hormone treatment on the results cannot be completely ruled out.

The relationship between prenatal androgens and sexual differentiation of the brain may also be studied in sex-typical cognitive abilities. Do individuals with GD show similarities in sex-typical cognitive functioning with their experienced gender or rather with their sex of birth? Preferably, sexual differentiation of cognitive functions should be studied in individuals with GD before the start of any treatment to ensure that findings cannot be explained by treatment effects (Kreukels & Cohen-Kettenis, 2012).

Cohen-Kettenis, van Goozen, Doorn, and Gooren (1998) found less functional cerebral asymmetry during processing of auditory verbal stimuli and better performance on a verbal memory task in MtF transsexuals compared to control men. FtMs also performed in a male-typical way on the verbal memory task. On sex-typical tasks, untreated MtFs and FtMs scored between male and female controls (Van Goozen, Slabbekoorn, Gooren, Sanders, & Cohen-Kettenis, 2002). A Norwegian study by Haraldsen, Opjordsmoen, Egeland, and Finset (2003) did, however, find a cognitive pattern consistent with birth sex in untreated individuals with GD before the start of treatment. Govier, Diamond, Wolowiec, and Slade (2010) suggest that there may be separate underlying etiological mechanisms in MtF and FtM conditions, based on results of a dichotic listening study. Overall, the neuropsychological findings provide some evidence for cross-sex indicators prior to gender reassignment.

In recent years, there has been a flurry of neuroimaging studies searching for biological mechanisms behind gender dysphoria. Some imaging studies do not find any evidence for a biological component in gender identity development and show that brain measures in individuals with GD do not differ from their sex of birth (Emory, Williams, Cole, Amparo, & Meyer, 1991; Savic & Arver, 2011). However, the study by Emory and colleagues was performed in treated transsexuals, and other studies before the start of treatment find greater similarities with the experienced gender for individuals with GD. Brain studies have focused on the size of the putamen, white matter microstructure, gray matter, cortical thickness, and functional activation patterns in response to various stimuli.

Several studies support the hypothesis for a sex-atypical differentiation of the brains of individuals with GD. First, FtMs differed from control women before the start of treatment in regional cerebral blood flow in the left anterior cingulate cortex and right insula (Nawata et al., 2010), and during mental rotation, untreated MtFs differed from control men in brain activation (Schöning et al., 2010). Second, similarities have been found between the brains of individuals with GD and their experienced gender in structure (white matter microstructure) in FtM transsexuals (Rametti, Carrillo, Gomez-Gil, Junque, Segovia et al., 2011) and function (hypothalamic activation) in response to odorous steroids in MtFs (Berglund, Lindstrom, Dhejne-Helmy, & Savic, 2008) and brain activation in response to erotic material in MtFs (Gizewski et al., 2009).

Brain measures may also show patterns that fall between those of men and women. Untreated androphilic MtFs show white matter microstructure patterns that differ from male *as well as* from female controls (Rametti, Carrillo, Gomez-Gil, Junque, Zubiarre-Elorza et al., 2011). In another study, untreated MtFs had similar volumes of gray matter compared to control men, but their putamen showed greater similarity with the female volume (Luders et al., 2009). Zubiaurre-Elorza et al. (2012) found a larger volume of the right putamen in FtMs compared to female controls, but no difference with male controls. This could be evidence for subcortical gray matter masculinization in FtMs. In MtFs, they showed that cortical thickness did not differ from female controls, but did from male controls, suggesting cortical thickness feminization in MtFs. These latter findings do indicate that different biological mechanisms may play a role in the etiology for FtM and MtF transsexualism.

Apart from etiological differences between MtF and FtM transsexualism, one might also discuss the findings of these neuroimaging studies in light of different typologies. Especially for MtF transsexualism, it is thought that there might be different developmental principles for subtypes with regard to sexual orientation (homosexual versus nonhomosexual) and onset age (early versus late onset of gender dysphoria). Although some of the abovementioned studies give information on onset age and sexual orientation and discuss their findings in light of these characteristics, others do not. The studies by the Spanish group (Rametti, Carrillo, Gomez-Gil, Junque, Segovia et al., 2011; Rametti, Carrillo, Gomez-Gil, Junque, Zubiarre-Elorza et al., 2011; Zubiaurre-Elorza et al., 2012) include only early-onset homosexual transsexuals, whereas the Swedish group (Berglund et al., 2008; Savic & Arver, 2011) only studies nonhomosexual transsexuals. The Spanish studies support the hypothesis for atypical sexual dimorphism of the brain in early-onset homosexual transsexuals. On the other hand, Savic and Arver (2011) found smaller volumes of the putamen and thalamus and greater volumes of gray matter in the temporoparietal junction and the insular and inferofrontal cortex in non-androphilic (nonhomosexual) MtFs compared to controls (men and women). These findings might also indicate a biological mechanism for gender dysphoria, although it certainly is a different mechanism than a sex-atypical dimorphism which is thought to underlie gender-dysphoric feelings. Together, the results of both groups are in line with Blanchard's idea that only the brains of homosexual transsexuals have developed in the direction of their experienced gender (Cantor, 2011).

All aforementioned studies were performed in adults with GD. In studies that did report onset age of the participants, it was retrospectively assessed. Our own group recently studied brain activation during verbal fluency in a group of adolescent, and thus early onset, individuals with GD (Soleman et al., 2013). We found a sex difference in activation in the right Rolandic operculum, an area adjacent to Broca's area during verbal fluency, and a trendwise linear increase in brain activation from control girls to FtMs to MtFs to control boys. Although these latter findings only approached significance, they again demonstrate brain activation patterns that fall between the sexes (Soleman et al., 2013).

In Chap. 2 of this volume, we have seen that heritability studies indicate that genetic factors probably play a role in gender development. A few studies found polymorphisms in sex steroid-related genes in transsexual groups (Bentz et al., 2008; Hare et al., 2009; Henningsson et al., 2005), but two other studies failed to find evidence for such polymorphisms (Bentz et al., 2007; Ujike et al., 2009). To further elucidate if and how genes influence gender identity, future studies should focus on direct effects of genes on the sex chromosomes on sexual differentiation and gender identity development, investigate epigenetic mechanisms, and apply genome-wide studies starting with the study of the sex chromosomes (see Chap. 2).

3.3.2 Psychological Factors

Psychological factors that play a role in the gender identity development of gender-variant children have always been a focus of investigation and hypothesizing. Zucker et al. (1999) administered the gender constancy interview (Slaby & Frey, 1975) in 206 clinically referred gender-dysphoric children (184 girls, 22 girls) and 95 controls (siblings, clinical referrals, and normal controls). This interview assesses the child's ability to identify the gender of dolls or photographs (gender discrimination), the child's own gender (gender identity), the child's own gender over time (gender stability), and the child's own gender with changes in clothing or behavior (gender consistency). Results showed that, in gender-dysphoric children, there was no qualitative difference in gender constancy development. Gender-referred children thus showed the same sequence when reaching the stages of gender labeling, gender stability, and gender constancy as found in normative samples (Slaby & Frey, 1975). However, the gender-referred children reached three stages of gender development, gender identity, gender stability, and gender consistency, later than controls. Additionally, in a free-play task, gender-referred children who had reported sex-normative gender consistency showed more same-sex play compared to the gender referrals who reported nonnormative gender consistency (Zucker et al., 1999). This finding is consistent with the literature on normative gender development, arguing that the acquisition of the ability to label gender is a prerequisite for developing gender-typed behavior (Ruble et al., 2006). Similar to the studies in normative gender development, the study in gender-referred children had a cross-sectional design and, therefore, does not provide evidence for the direction of the effect between gender constancy development and sex-typed behavior. This might be different in normative gender development compared to gender-variant development. As Zucker et al. (1999) suggests in discussing his findings, it might be that in gender-dysphoric children, the different patterns of gender self-labeling have a different meaning and are not randomly made. It might be that there is not an underlying cognitive developmental lag, but rather the incongruence between natal and experienced gender. Also, it may be that cross-gender behavior promotes or encourages self-labeling. Indeed, in clinical practice many (not all) parents have early narratives of their gender-dysphoric child expressing strong cross-gender behavior as early as age two or three and insisting to be the other gender at one time. By the time they go to the gender identity clinic, most gender-dysphoric children are perfectly able to label their own gender according to their natal gender, which they strongly dislike while expressing that they want to be the other gender. They may even express anatomic dysphoria (“I do not want to have a penis” or “I do not want to have breasts”) (Cohen-Kettenis, 2005).

In terms of gender-variant development, older studies suggested that GD is part of a more pervasive psychological disturbance (Coates & Person, 1985). It has been postulated that an anxious temperament of the child interacting with certain parental factors and a child’s predisposition to cross-gender behavior might lead to the development of gender dysphoria (Zucker & Bradley, 1995). There are indeed studies that show high prevalence rates of separation anxiety traits (Zucker, Bradley, & Lowry Sullivan, 1996) and other internalizing problem behavior in referred gender-dysphoric children (Cohen-Kettenis, Owen, Kaijser, Bradley, & Zucker, 2003; Wallien, Swaab, & Cohen-Kettenis, 2007). In these studies, however, a putative temporal direction between anxiety or internalizing problem behavior and gender dysphoria cannot be determined. It might be that clinic-referred gender-dysphoric children will be anxious in later childhood because they are at risk for developing self-esteem problems. A recent study in 147 referred gender-dysphoric children on self-perception showed that, compared to the Dutch norms, they had low scores on various dimensions of self-concept (global self-worth and physical appearance among others) (Rijn, Steensma, Kreukels, & Cohen-Kettenis, 2012). This finding correlates with the aforementioned findings from general population samples indicating that a combination of low gender typicality and high felt pressure to conform to gender stereotypes is predictive of internalizing problems (Yunger, Carver, & Perry, 2004).

In most prepubertal children, gender dysphoria will remit, while in a minority it will persist after puberty (e.g., Drummond et al. 2008; Singh, 2012; Steensma et al., 2013; Wallien & Cohen-Kettenis, 2008) and only be resolved by gender reassignment (e.g., Cohen-Kettenis & van Goozen, 1997; Smith, Van Goozen, Kuiper, & Cohen-Kettenis, 2005). One recent qualitative study compared three factors that emerge between the ages of 10 and 13 that seem crucial in whether gender dysphoria persists or remits. These were changing social environment (the social pressure to conform to gender stereotypes increased), the anticipated or experienced bodily changes of puberty, and first experiences with falling in love and sexual attraction (Steensma, Biemond, Boer, & Cohen-Kettenis, 2011).

3.3.3 Social Factors

In the 1950s, Money and his colleagues, who were the first to conduct follow-up studies among patients with DSD, concluded that gender identity largely followed the gender of rearing and that nurture overruled nature in establishing gender identity (Blizzard, 2002; Meyer-Bahlburg, 1998; Money et al., 1955). Although Money always acknowledged the importance of biological factors (hormones and genes) in gender identity development (Money, Ehrhardt, & Masica, 1968), he assumed that early (preferably not later than 24 months) gender reassignment and accompanying surgery creating sex-compatible external genitalia would enable the child to label himself/herself cognitively as a boy or a girl and develop a male or female self-image (Blizzard, 2002; Money et al., 1955). Later research, however, has provided evidence that biological factors are in many cases of larger importance and children with DSD who were raised according to Money's "optimal gender policy" sometimes developed gender identity problems. Despite this, in a review of gender identity outcomes in various DSD, gender change after a chromosomally opposite gender assignment occurred in only 42 % of cases, with considerable variability across DSD (0–80 % range). In most cases, the best predictor of gender identity outcome in adulthood remained the initial gender assignment. This suggests that gender assignment (which may include early childhood medical intervention such as gonadectomy), together with concomitant social and psychological factors, has influence on gender identity outcome (De Vries et al., 2007). Because many factors, including cultural and historical-sociological ones, are involved in gender assignment at birth in individuals with DSD, assumed contributions of environmental factors versus early medical interventions when DSD individuals persist with a chromosomally opposite gender assignment can only be interpreted cautiously.

In the older literature on the development of gender dysphoria in non-DSD children, social factors such as a maternal wish for a daughter, paternal absence, parental reinforcement patterns, or a symbiotic relationship between mother and son were considered of significant importance (e.g., Green, 1974; Stoller, 1968). More recent theories suggesting that parental psychopathology might partly influence gender-variant development have received only minimal empirical evidence. In these theories, parents' emotional unavailability might hamper healthy limit setting and cross-genderedness might be encouraged (Zucker & Bradley, 1995). However, a study investigating the presence of psychological problems in parents of gender-dysphoric children revealed only mild depressive symptoms in the mothers, but no other indications of serious parental psychopathology (Wallien, 2008).

3.4 An Integrative Biopsychosocial Perspective on Gender-Variant Behavior

In their review on transsexualism, published more than a decade ago, Cohen-Kettenis and Gooren (1999) wrote: *"Adult gender identity and gender role behavior develop gradually over a long period of time and are influenced by multiple, interacting factors, active at different developmental periods… Our understanding of this process has increased considerably, but a large part of it still remains enigmatic."* How far have we come since then? From the previous sections in this chapter as well as from Chaps. 1 and 2, we can conclude that there is evidence that biological, psychological, and social factors are all influential in determining not only how one's gender identity is resolved but also the degree of gender-typical or gender-atypical behavior that is displayed.

The role of nature versus nurture has always been debated in studies of psychological characteristics in humans, and this is to an even larger extent true for their respective roles in gender (identity) development and gender dysphoria. At present time, the generally accepted view is that a complex interplay between genetic (nature) and environmental (nurture; social and biological) factors leads to individual behavioral differences (e.g., Lenroot & Giedd, 2011). The various family (mostly twin) studies that are presented in Chap. 2 show a considerable heritability of gender-related traits within sexes (heritability estimates for gender dysphoria varied from 0.22 to 0.77, although in population studies, it is probably not gender dysphoria that is measured, but gender variance). These studies demonstrate the fact that with regard to gender dysphoria, the same complex interaction between nature and nurture exists.

3.4.1 Interacting Biological, Psychological, and Social Factors

The studies described above have begun to identify how some characteristics of development such as brain functioning and cognitive representations differ for gender-variant individuals, as well as possible links to these factors. What is not known is how these factors work together to influence gender identity development. For instance, how might the experience of being reared in a more or less stereotypical household interact with levels of prenatal androgen exposure to influence variability in identity as well as gender role beliefs?

One such study using sex hormone binding globulin levels measured during the first trimester of pregnancy as a measure for prenatal testosterone exposure found an association between these levels, parental encouragement of feminine behavior in childhood and gendered behavior in adult women. Adult women with the highest prenatal testosterone exposure were least susceptible to their mothers' encouraged femininity in childhood (and displayed the least feminine behavior), whereas women of mothers with the lowest testosterone levels were most feminine and only then did parental encouragement affect feminine behavior (Udry, 2000).

In more traditional cultures that still value the male over the female role, transitions to the male role in individuals with 5α-RD-2 deficiency after the rise of testosterone levels in puberty and its virilizing effects are more common (Hughes et al., 2006). This implies that both biological factors and cultural ones are important.

An interaction between psychological and social aspects of gender identity has long been found in population-based studies of gender conformity; gender nonconformity is more distressing for children who experience high pressure to conform to gender norms (Carver et al., 2003). A current study has expanded this concept to examine the role of contentedness with assigned gender, gender-atypical friendship styles, and adjustment (Menon, 2011). For girls in particular, gender contentedness was associated with better adjustment, even in the context of gender-atypical peer relationship styles which were associated with less adjustment. For boys, the role of contentedness was less clear (Menon, 2011). Studies such as these reveal the importance of combining multiple indicators of well-being and examining the role of gender identity in multifaceted ways. Children who feel more comfortable with their gender identity may have better resilience to cope with their own gender-atypical behaviors.

3.4.2 Gender-Normative Versus Gender-Variant Development

Prior research efforts have been largely divergent in studying either gender-typical-normative or gender-variant nonconforming development. The merging of these two lines of inquiry may help to reveal processes and interactions among developmental forces that influence gender identity development across the entire range. The final section of this chapter is focused on what we have come to learn about the various interacting developmental influences, considering the ways in which each line of study (i.e., gender-normative versus gender-variant development) can inform the other and identifying future areas of research.

Most studies on normative gender (identity) development to date have focused on "universal" and "average" developmental trends and average times when "gendered" milestones occur as well as average differences between groups, instead of delineating the range of experiences within a population. This approach has gone as far as to suggest that children who do not develop a particular concept have "failed" a developmental task. For instance, part of the theory on gender identity development is that all children will develop a belief that gender cannot be changed (gender constancy) (Kohlberg, 1966). A child who holds an alternative perspective would be considered incorrect or delayed in development, although it is recognized that the empirical support for this concept has been weak (Ruble et al., 2006).

Research evidence, clinical experience, and research with children, adolescents, and adults with GD have shown that variability exists around the ways in which people define and label their own gender identity and experience gender as permanent or changeable over time. There may be children who believe they are a gender other than the one typically assigned based on genital appearance. There may also be children who believe they will grow up to be a gender different than the one they currently are. Children who report that gender can change over time might not understand that changing gender is a lengthy and uncommon process (i.e., they might not yet have the cognitive skills to understand this), or they may represent one small part of the population that experiences gender as something changeable.

According to cognitive theories of gender, these gender-dysphoric children would be classified as having a “developmental lag” in achieving the phase of “gender constancy” (Zucker et al., 1999). However, it can also be that these children refer to the possibility of gender reassignment, a possibility that some children are aware of at a very young age (Cohen-Kettenis & Pfäfflin, 2003). At this point in time, we do not know the underlying motivation that drives a gender-dysphoric child to this belief of being the other gender (Zucker et al., 1999), but initial research has discovered that children with this belief are far more likely to request gender reassignment as adolescents. That is, although gender dysphoria will remit in most prepubertal children, Steensma et al. (2013) found in their prospective follow-up study that, among children who were interviewed with the Gender Identity Interview for children (Wallien et al., 2009; Zucker et al., 1993) and asked with what sex they identified as “I am a boy” or “I am a girl,” the children who expressed a cross-gender identification had a greater chance of persisting gender dysphoria.

Furthermore, in the gender constancy theory, the labeling of gender is often linked to genitals (e.g., girls have a vagina), which does not allow for cognitive flexibility or account for variability based on the presence, absence, or characteristics of the genitals. Psychosexual outcome studies of individuals with DSD have helped to shift concepts of gender identity away from purely genital definitions, but the general notion remains that gender identity is unalterable. When someone is born with ambiguous genitals, as may be the case in individuals with DSD, a variety of other characteristics are used to interpret the development of a gender identity. According to Money’s (1955) optimal sex policy and Kohlberg’s (1966) gender constancy theory, children who are taught that someone is a man if he has a penis and understand that this concept is considered fundamental to cognitive development will not have the opportunity to develop a more flexible view of what defines gender. For example, children performing a classical gender constancy task are not asked to consider other indicators of maleness or femaleness, such as clothing, mannerisms, and self-reported identity. More modern theories of gender identity development incorporate aspects such as contentedness with gender and understanding of pressure to conform to stereotypes (Egan & Perry, 2001) but still generally expect that children understand that the gender assigned at birth will not change.

Contrary to this developmental expectation, we know that gender does change over time for some people, i.e., individuals who undergo sex reassignment or who begin to identify with a gender other than the one into which they were born. Such individuals might require support and medical interventions to develop a body that is consistent with their internal gender identity, or they might experience an internal gender identity that develops and changes over time in a more fluid manner but experience a gender that changes over time. Only when developmental theories account for alternative pathways of development will it be possible to fully understand the biological, psychological, and social factors that contribute to the development of gender identity and how it may change or not over time for different people.

Only recently, research on gender nonconformity and gender dysphoria has begun to examine the extent to which individuals may transition completely from one gender to another or may instead identify as a third gender or gender queer (Bockting & Ehrbar, 2005). Some gender-dysphoric children and adolescents describe discomfort with a binary system of gender that expects people to fall within socially prescribed norms for male or female. This group may not necessarily struggle with a sense of being in the wrong body, but rather struggle with an inability to conform to rigid binary gender expectations (Bockting & Ehrbar, 2005; Kessler & McKenna, 2000; Lombardi, 2009). What is not known about third gender identity is the extent to which it may be influenced by the accessibility and affordability of gender reassignment treatment, the social support for or against gender reassignment, or the societal willingness to accept individuals with an ambiguous gender. To be certain, the concept of third gender identity is represented in queer theories (Kessler & McKenna, 2000) and community-based studies in North America (Bockting & Ehrbar, 2005; Lombardi, 2009; McGuire & Conover-Williams, 2010; Menvielle & Rodnan, 2011) and appears less frequently in the research based on clinical studies. A major unknown factor for understanding third gender identities includes the role of societal acceptance (or not) of nonrigid gender binaries. In a society that expects rigid gender binaries, will individuals be more likely to make complete transitions than those in a society more willing to allow individuals to inhabit a space between male and female? The biological, psychological, and social factors associated with third gender identities represent an area of future research that, if fully explored, should assist us in better understanding the full spectrum of gender identity development.

3.5 Future Directions

Behavioral genetic studies of gender identity have provided us with some information on the relative contribution of genetics to gender identity development. As with most features of development, gender identity is complex and genetic contributions likely exist across multiple genes. As described in Chap. 2, some association studies have been performed that investigated candidate genes for transsexualism. Given the importance that androgens and estrogens play in the sex differentiation of the brain (see above, this chapter), genes that are involved in either sex steroid biosynthesis or action are the focus of investigation. In the small number of studies performed, only two polymorphisms appeared to show an association with transsexualism: in CYP17 in FtM transsexualism (Bentz et al., 2008) and in AR in MtF transsexuals (Hare et al. 2009; Henningsson et al. 2005). Klink and Den Heijer conclude that "… *no strong candidate gene has emerged for the development of gender dysphoria. Because of the complexity of gender identity development it does not seem likely that one single gene will be discovered. Gender identity is such a robust and prominent trait that polymorphisms of genes alone are unlikely to account for the development of gender dysphoria"* (Chap. 2).

Clearly, future studies will focus on genes that are involved in gender identity development. How will these studies help us in understanding determinants of gender identity development? Are psychological and social factors still of relevance, or are biological determinants so important that we do not have to consider psychological and social factors any longer?

Studies of gene × environment interactions have not extended into the gender identity realm yet, but the groundbreaking study of the role of the serotonin transporter gene (5-HTT) suggests that, for some individuals, a genetic predisposition (the short allele variation of the 5-HTT gene) must be coupled with an aversive environmental exposure (child maltreatment) in order to elicit certain characteristics (depression) (Caspi et al., 2003). A decade after the publication of this study, gene environment research has been a hot topic, as indicated by the large number of publications in high-impact journals. However, their original promise has been tempered and criticized, as finding specific gene environment interactions and replicating them turns out to be extremely complex due to the large number of factors that are involved (Duncan & Keller, 2011). Apart from genes and environment, behavioral outcome is also determined by the timing of the interaction, resulting in an age x gene x environment interaction (Lenroot & Giedd, 2011). With regard to gender identity development, it has been suggested, for example, that gender identity is malleable at a certain young age but becomes "fixed" and unalterable after adolescence (Zucker, 2004).

We have come to recognize that no one etiological factor can account for transsexualism. As described before, neuroimaging studies in gender-variant people may also help us in elucidating the mechanisms behind gender identity development. A specific group of interest may be that of people with Alternating Gender Incongruity, a subcategory of *bigenders* who experience alternating gender states (Case & Ramachandran, 2012). Gender-dysphoric feelings may be a result of the difference between the brain's gender and the "sex" of the body. Neuroimaging studies have shown evidence for sex-atypical differentiation of the brain in at least certain subgroups (early-onset "homosexual") of people with GD. A different mechanism may be behind gender dysphoria in transsexuals attracted to the gender other than their natal one. A magnetic resonance study showed differences in the brain between these MtF transsexuals and male and female controls (Savic & Arver, 2011). Future neuroimaging studies should further focus on the mechanisms that underlie these differences in various subgroups of transsexuals.

In order to disentangle the contribution of the different factors involved in gender identity development, we thus have to take into consideration that the gender dysphoria phenomenon by itself is not a homogeneous condition but consists of different subtypes. For example, as pointed out before, age of onset and sexual orientation might differentiate subtypes, but comorbid conditions, such as autism spectrum disorders, might also reflect that different causal developmental pathways can lead to the final outcome of gender dysphoria (e.g., De Vries, Noens, Cohen-Kettenis, van Berckelaer-Onnes, & Doreleijers, 2010). In addition, it is important to elucidate what the resemblances and differences are of individuals exhibiting gender nonconforming behavior and those with an explicit desire for gender reassignment treatment. Are these distinct groups or are they both part of a more or less continuous gender dysphoria phenomenon?

Future studies of gender identity development should not only seek to understand the potential genetic and environmental (both from nature and nurture) factors in the development of gender identity but also when these factors emerge in life and how those factors may have differential influence at different points along the spectrum of gender dysphoria.

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Part II
Disorders of Sex Development

Chapter 4
The Early Care of the Infant with a Suspected Disorder of Sex Development

S. Faisal Ahmed

Abstract Disorders of sex development (DSD) are a wide range of relatively rare conditions with diverse pathophysiology that are most often present in the newborn or the adolescent. Given their rarity and the need for multidisciplinary input, the management of the child with a complex form of DSD may be quite complex, and the situation is worsened by the lack of evidence of many diagnostic and interventional procedures that are undertaken. It is, therefore, not surprising that there will be variation in management as well as outcome of patients with this group of conditions. Whilst variation in clinical practice may reflect on the quality of care, this link still needs careful exploration in the field of DSD. By working as a network of clinical and research centers, it is possible that these variations can themselves be better managed and studied. This chapter will concentrate on outlining the variation in the early care and evaluation of infants with suspected DSD.

4.1 Introduction

Truly ambiguous genitalia on expert examination are a particularly challenging problem, but this situation is relatively rare and reported to occur in about 1:4,500 births (Thyen, Lanz, Holterhus, & Hiort, 2006). However, a concern about the development of the external genitalia may exist in 1 in 300 newborn infants, and, in over 80 % of cases, the affected infants are raised as boys and are likely to have a chromosome complement of 46,XY (Ahmed et al., 2004). Thus, it is estimated that in a country such as Scotland with 58,000 births per year, 200 infants are born with atypical genitalia and 160 are raised as boys. In girls with 46,XY karyotype, the

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most common known genetic condition that leads to a DSD is congenital adrenal hyperplasia due to 21α-hydroxylase which occurs approximately in 1:14,000 infants, and each year Scotland would expect to have approximately two affected girls. Unlike infants with XX DSD, who are most likely to be clinically investigated comprehensively and, in over 90 % of cases, shall have congenital adrenal hyperplasia, many infants with XY DSD who are raised as boys are investigated to a variable extent and the etiology remains unclear in the majority of them.

4.2 Variation in Terminology and the Chicago Consensus

The use of terminology which is clear and easy to use and understand by all health professionals, patients, and their families is fundamental to the understanding, investigation, and management of affected newborns and children. In addition, terminology should respect the individual and avoid terms which might cause offense. The term "intersex" has had variable connotations even within professionals; some employed it as a term that covered all affected newborns whilst, at the other end of the spectrum, some believed that the term should only apply to those in whom there is complete mismatch between chromosomal and anatomic sex. The consensus reached at the meeting of the Lawson Wilkins Pediatric Endocrine Society and the European Society for Pediatric Endocrinology in 2005 in Chicago on the management of these patients, stressed the importance of terminology, and recommended the substitution of the term "intersex" with "DSD," which is defined as any congenital condition in which development of chromosomal, gonadal, or anatomic sex is atypical (Hughes, Houk, Ahmed, Lee, & The LWPES/ESPE Consensus Group, 2006). It also recommended the abandonment of terms such as "pseudohermaphroditism" and "true hermaphroditism." One of the greatest strengths of the new nomenclature is that it guides the clinician in reaching a definitive diagnosis in a stepwise manner. For instance, a child with a small phallus and penoscrotal hypospadias who has a 46,XY karyotype may initially be labeled as 46,XY DSD, but, as he undergoes investigations, he is suspected to have a disorder of testosterone synthesis. The biochemical tests may point toward a deficiency of 17βHSD, and the diagnosis is confirmed by genetic investigations.

Although the DSD nomenclature (see Table 4.1) is easier to use and understand, and helps the professional in planning investigations, it will nevertheless evolve over time as our understanding of long-term outcome, as well as molecular etiology, improves in the future. The structure of the nomenclature has been developed in such a way that there is scope for it to incorporate such developments. Given that genital anomalies may occur as commonly as 1 in 300 births and may not always be associated with a functional abnormality, some have advocated the use of "differences" in preference to the term "disorder" (Diamond, 2009). The use of phrases such as "differences" or "variations" in sex development may help to introduce the concept of the range of variation that may occur in sex development. The strength of the acronym "DSD" is that it can be used to cover both differences and disorders

Table 4.1 The range of disorders of sex development that may be associated with a male sex of rearing

Disorder type	Diagnosis
XX or XY disorder of gonadal development	Complete gonadal dysgenesis
	Partial gonadal dysgenesis
	Gonadal regression
	Ovotesticular DSD
	Testicular DSD
XY disorder of androgen synthesis	Lipoid congenital adrenal hyperplasia*
	P450 side chain cleavage enzyme deficiency*
	3β-Hydroxysteroid dehydrogenase 2 deficiency
	17,20-Lyase deficiency
	17β-Hydroxysteroid dehydrogenase 3 deficiency
	5α-Reductase-2 deficiency
	P450 oxidoreductase deficiency
XY disorder of androgen action	Complete androgen insensitivity syndrome
	Partial androgen insensitivity syndrome
XX disorder of androgen excess	21α-Hydroxylase deficiency*
	11β-Hydroxylase deficiency*
	P450 aromatase*
	P450 oxidoreductase deficiency*
XY Leydig cell defect	Leydig cell hypoplasia
	LH deficiency
XY persistent Mullerian duct syndrome	AMH low
	AMH normal
XY isolated disorders of genital development	Isolated hypospadias
	Isolated bilateral cryptorchidism
	Isolated micropenis
XY complex disorders of genital development	Cloacal anomaly
	Bladder exstrophy
	Complex syndromes
	Complex combined anomalies

Conditions marked with an asterisk are more likely to be associated with a female sex of rearing. Further clinical details of the commonly encountered conditions are available in Ahmed et al. (2011)

of sex development. However, the likelihood of this difference existing as a disorder will depend on the functional implications of the condition, which may also be heavily influenced by the social and cultural framework within which the child exists.

4.3 Variation in Investigating Infants at Initial Presentation

While there is no doubt that investigations are required in all infants with clearly ambiguous genitalia in whom the sex of rearing is uncertain, there is less clarity about when investigations should be performed in those situations in which the genitalia are less ambiguous. This is particularly the case in those infants who are considered to be boys. Although there are some guidelines to inform the clinician's decision to investigate, these are mostly based on expert opinion (Hiort, 2011; Keir, O'Toole, Robertson, Wallace, & Ahmed, 2009; Viner, Teoh, Williams, Patterson, & Hughes, 1997). These guidelines suggested that groups of infants who should be evaluated include those with female genitalia with atypical features, such as an enlarged clitoris, or those with male genitalia with atypical features, such as abnormal penile development or impalpable testes. An evaluation may also be necessary in those with a family history of DSD or when there is a discordance between genital appearance and a prenatal karyotype.

In suspected cases of DSD, a karyotype check is often the first test that is undertaken; studying the practice of performing a karyotype in cases of atypical genitalia may be one way of assessing the variation in the practice of investigating new infants. A review by Rodie et al. (2011) of the practice of performing karyotype in Scotland, using the register kept by the Scottish DSD Network, showed that of 572 affected cases presenting between 2002 and 2007, 153 had a karyotype. This was more likely in the presence of a low masculinization score, bilateral impalpable testes, proximal hypospadias, or associated malformations. This study had primarily collected data from two Scottish cities with a combined birth rate of 16,500/year. Of the 572 cases, 52 had a karyotype within the first 10 days of birth and 20 of these 52 cases had it performed urgently, suggesting that there was a question about sex assignment in these 20 cases. Thus, these data also suggest that approximately three out of 16,500 births per year require further tests for sex assignment. The study also showed that 20 % of boys with bilateral impalpable testes did not have a karyotype, and in most karyotyped cases, this was performed after the age of 10 days.

4.4 Variation in Diagnostic Investigations

Reaching a diagnosis in DSD requires thorough delineation of the external and internal anatomy, as well as biochemical and molecular genetics. Not only are these procedures dependent on the skills and knowledge of the operators, but they are also highly resource intensive and continue to evolve over time. Biochemical tests are highly dependent on the method used to perform the test (Tomlinson, Macintyre, Dorrian, Ahmed, & Wallace, 2004). By identifying the etiology more precisely, molecular genetic analysis has the potential to tailor the rationale for long-term therapy and management in many cases of DSD, but there is a need to show this more clearly by reporting long-term outcome (Camats et al., 2012; Tantawy et al., 2012). Notwithstanding these challenges, it is clear that the range of tests that are performed in cases of DSD can be quite variable. This was illustrated when studying a research database of over 700 cases of XY DSD that was held in Cambridge in 2000 (Ahmed, Cheng, & Hughes, 1999). This database consisted primarily of cases from a wide range of clinicians in the UK. Of 153 cases suspected of having partial androgen insensitivity syndrome, approximately one third did not undergo stimulation with human chorionic gonadotrophin (hCG), a test which is performed to study the production of testosterone so that conditions which are associated with poor testosterone synthesis can be identified. Furthermore, a range of doses of hCG were administered in those who did have an hCG stimulation test (Ahmed et al., 1999). The regimen of hCG stimulation and the timing of the blood samples may be important in the interpretation of the test, as reported by Dixon, Wallace, O'Toole, and Ahmed (2007). The definition of an optimal testosterone response to hCG stimulation has also been variable (Kolon & Miller, 2001).

4.5 Variation in the Support Available to New Parents

Child behavior, life events, and parental personality characteristics can raise parenting stress which, in turn, can adversely affect the quality of caregiving, parent–child interactions, and child behavior (Dawson, Ashman, & Carver, 2000). Coping is used to mediate stress, and a family can utilize specific cognitive and behavioral coping strategies to reduce this stress. It is likely that parenting stress and coping patterns may influence the child's long-term psychological outcome. Whilst there are many published reports of the role of chronic disease as parental stressors, there is little published evidence on the needs of parents of children with atypical genitalia and how best to support them. As it is important to understand potential stressors that parents may face and the methods they use to cope with their child's condition, the Scottish DSD network performed a study in 2004 examining stress and coping patterns among parents of affected children using quantitative psychological assessment tools, as well as a semi-structured qualitative interview. Quantitative assessment results indicated that parents did not generally seem to display abnormal levels of stress or coping (Duguid et al., 2007). However, the semi-structured interview provided further information about the parents' level of coping and potential for stress and highlighted the need for more effective exchange of clinical information. The study also raised a question about the reliability of using standardized quantitative questionnaires for the purpose of identifying parents with clinical levels of stress or problems with coping. Of the 19 parents who were interviewed, 95 % reported receiving suboptimal information at birth, 84 % had concerns about sexual function and fertility, 80 % found relatives a helpful source of support, and approximately 75 % found senior hospital-based clinical staff a useful source of support. However, about 65 % also reported that they found the subject difficult to discuss with relatives and friends, and approximately 60 % coped with the condition by thinking that it could be completely treated. In addition, four parents admitted that the condition was even difficult to discuss between the mother and father, and four wished for greater support in explaining the condition to the affected child. Eleven (58 %) parents reported that they were unclear about the expected appearance of the genitalia following the operation. Five (26 %) parents raised concerns about recurrence of the condition either in their own future offspring or those of the affected child or the affected child's siblings. A substantial number of parents reported the need for written information on general issues such as the condition. The need for gradual and steady information about the condition following the initial presentation was also reported, as was the need for some illustrative examples of the expected appearance postoperatively. Eight (42 %) parents reported the desire to have a local network of families with children affected with similar conditions. Other sources of support such as a website and a link person who would be available at the initial presentation were also highlighted by some parents.

In 2011, a revised survey was performed to assess similar outcomes. The questionnaire was administered, by post, to all parents of children between the ages of 6 months and 24 months on the Scottish DSD Network register. Of the 56 questionnaires sent to families whose children had been managed in four centers in Scotland, 17 (21 %) completed questionnaires were received from parents with babies delivered in 10 maternity hospitals in Scotland. The sample was largely made up of boys with hypospadias, and only one parent was aware of a delay in sex assignment of their child. For most outcomes, the care received was rated favorably, but the availability of emotional support and information through websites and support groups was rated low by many parents (unpublished observations).

4.6 UK Guidance on the Initial Approach to an Affected Infant

Based on the above findings, a UK taskforce representing the wide range of professionals who are often involved in a complex case of DSD developed and published some guidance that was aimed at supporting clinical professionals in the initial evaluation and diagnosis of children with suspected disorders of sex development and providing a framework to standardize clinical practice throughout the UK. The consensus that was reached in Chicago in 2005 on the general principles of managing patients with DSD represented a historic milestone for international and multidisciplinary collaboration in this area. However, some areas of care, such as the initial approach to evaluating the infant or young person with suspected DSD, were not covered in detail as that was beyond the scope of the exercise. In addition, guidance on the initial evaluation of a complex condition is often colored by local provision of health care, and it was felt that reaching a consensus at a national, United Kingdom, level would be the most effective means of proceeding further. The guidance was subjected to a lengthy period of open consultation before its publication (Ahmed et al., 2011). The main recommendations are summarized as follows:

- Infants with a suspected DSD should be treated by an experienced multidisciplinary team, accessible through a regional center. At a minimum, this team should include specialists in endocrinology, surgery and/or urology, clinical psychology, radiology, nursing, and neonatology.
- One main contact person should be assigned to each family; in most cases, this will be the pediatric endocrinologist. The family should be told of the range of support available to them and provided with contact details for these personnel. They should also be made aware of the stepwise process used to diagnose and manage DSD, with the ultimate goal of achieving long-term well-being.
- Access to specialist psychological support during and after the diagnostic process is essential for both the affected person and their parents. The pace of how information is shared should be set by the family and issues of confidentiality discussed and respected.
- The exact tests used to diagnose a DSD will vary among patients. However, at a minimum, the multidisciplinary team should take into account the patient's external appearance, internal anatomy, genetic makeup, and hormone profile.
- The most important goals of the initial assessment period are to support the affected child and parents, assign a sex of rearing, and exclude the possibility of any early medical problems.
- Patient groups can provide important psychological support and information to affected individuals and their families. Contact details of relevant support groups should be provided as routine by healthcare professionals upon diagnosis.
- All medical personnel involved in the care of a patient with a DSD should have access to a regional DSD team. The team has a responsibility to educate other healthcare staff and should have a regular forum where they meet to discuss the case and review its own performance.
- By contributing to national and international disease registers, regional DSD teams have an important role in performing audit and research into the long-term outcome of these rare conditions.

4.7 Clinical Networks for Managing Complex Conditions

It is unrealistic to expect that every major clinical center can possess a comprehensive, multidisciplinary DSD team as outlined earlier. Furthermore, in many cases, care at a local hospital may be more appropriate for reasons of both convenience and necessity (e.g., adrenal crisis in CAH). For the less complex case of hypospadias, immediate multidisciplinary input may not be necessary, and initial discussion and explanation of the condition with the parents do not require urgent transfer of the baby at an emotionally sensitive period. Similarly, some investigations can also be performed at local centers that are affiliated to a regional center. It is, however, important that all personnel who may be involved in the care of an affected person have access to the regional DSD team and have the opportunity to develop themselves professionally. Some regions have overcome these hurdles with the

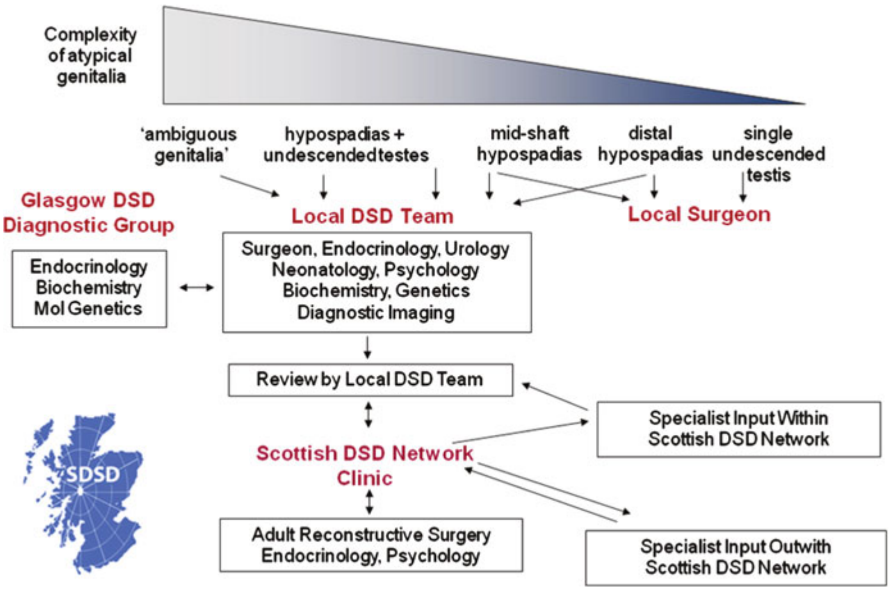
Complexity of atypical genitalia
'ambiguous genitalia'
hypospadias + undescendedtestes
mid-shaft hypospadias
distal hypospadias
single undescended testis
Glasgow DSD Diagnostic Group
Local DSD Team
Local Surgeon
Endocrinology
Biochemistry
Mol Genetics
Surgeon, Endocrinology, Urology
Neonatology, Psychology
Biochemistry, Genetics
Diagnostic Imaging
Review by Local DSD Team
Specialist Input Within Scottish DSD Network
Scottish DSD Network Clinic
SDSD
Adult Reconstructive Surgery
Endocrinology, Psychology
Specialist Input Outwith Scottish DSD Network

Fig. 4.1 Structure of the service that the Scottish DSD Network aims to deliver in Scotland. Depending on the complexity of the condition and the individual needs of the patient, the patients flow between clinics where healthcare professionals with appropriate skills are available. The network is supported by a diagnostic group which meets separately, channels cases for molecular genetic evaluation, and interprets the results

development of a national managed clinical network (http://www.sdsd.scot.nhs.uk). A service model such as this attempts to provide an equitable state-of-the-art service for all affected children and adolescents in a region. A formal organization allows a structured referral pathway within the region, as well as beyond, and provides the infrastructure for better long-term care of the patient as close to home as possible (see Fig. 4.1). A network can also facilitate the creation of agreed protocols for the care of the affected newborn, setting and monitoring of national standards of care, and rational utilization of other services such as molecular genetics and clinical biochemistry and provides a forum for education and professional development.

Research and audit are vital for the management of DSD, and clinical networks have a strong potential to drive these activities. The 2005 Consensus Meeting on DSD stressed the need for the creation and maintenance of a database in centers of expertise. Clinical audit systems that collect information on clinical activity and outcome should be an integral component of national specialist services and need to be seen as a tool for management, as well as audit. Such databases may exist at a less formal level in many other regional centers but until recently have lacked international uniformity and the ability to cross talk. A Web-based register (http://www.i-dsd.org) has been approved by the UK National Research Ethics Service as a multicenter research database which does not require any further local research approvals but does require the approval of the patient or parent. The development of this Web-based virtual research environment was initially supported by the European Society of Paediatric Endocrinology in 2007 as the European DSD Registry. Following this, it was further developed between 2008 and 2011 by the EuroDSD project (Ahmed, Rodie, Jiang, & Sinnott, 2010), and it is now supported by the Medical Research Council of the UK as the International DSD Registry. Clinicians from 28 countries from the 5 continents have now registered as users of this Registry, and, currently, 19 clinicians from 14 countries in 3 continents (Europe, Asia, and Africa) have contributed clinical details in 1,098 cases. It is anticipated that the Registry will act as a long-term resource that supports the development of an international clinical and research network.

4.8 Conclusion

The last decade has seen enormous strides toward the development of multicenter collaboration—a willingness of experts in the field of DSD to reach a consensus and develop clinical and research networks. This has coincided with major advances in our knowledge of the underlying etiology as well as the diagnostic technology that is currently available now. It is anticipated that these developments that focus on the early care of the affected child will lead to an improvement in long-term outcome. The ground is now set for the wider community of healthcare professionals and patients to agree on the long-term outcomes that need to be assessed. Finally, while there is a high level of agreement on the importance of communication within clinical teams, as well as between the teams and the patients and their parents, there is a need to improve our understanding of effective methods of communication.

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Chapter 5
A Noncategorical Approach to the Psychosocial Care of Persons with DSD and Their Families

David E. Sandberg and Tom Mazur

Abstract The 2006 Consensus Statement on Management of Intersex Disorders incorporated all variations in sex development under one superordinate term, disorders of sex development (DSD), and called for care to be delivered by integrated teams that include behavioral health providers. This chapter proposes an integrated team care model that is patient and family centered and attempts to balance the dominating perspective that focuses almost exclusively on gender-related aspects of DSD with one that conceptualizes DSD as a congenital and chronic condition, akin to other pediatric conditions. Ideal DSD team structure and functions are described; emphasis is placed on integrating services and enhancing communication among members of the healthcare team and the family. Evaluation and treatment issues are identified, as well as the need for routine reassessment, given that the importance of particular domains (e.g., sharing information, fertility) varies with developmental stage. A strategy for selecting assessment instruments is outlined, and links are provided to databases of psychometrically robust measures of health-related quality of life as well as narrower domains of function. Because confusion remains, distinctions between DSD and transsexualism are delineated. Finally, barriers to the implementation of the proposed model are considered.

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5.1 Introduction

In 2005, international healthcare experts, researchers, and patient advocates assembled in Chicago to formulate a consensus document on the clinical management of individuals born with intersex conditions. The *Consensus Statement on Management of Intersex Disorders*, published in 2006, recommended eliminating confusing and potentially stigmatizing terms such as "intersex," "pseudohermaphroditism," "hermaphroditism," and "sex reversal" to refer to these conditions (Lee, Houk, Ahmed, Hughes, & in collaboration with the participants in the International Consensus Conference on Intersex, 2006). The conference summary (hereafter referred to as the Consensus Statement) incorporated all variations in sex development under one superordinate term, disorders of sex development (DSD), defined as "congenital conditions in which development of chromosomal, gonadal, or anatomic sex is atypical." This move allows us to shed the simplistic notion that gonads are the only parameter defining sex. Despite rapid and broad acceptance of the DSD nomenclature, there remain disagreements regarding whether specific syndromes (i.e., Turner syndrome and Klinefelter syndrome) and particular genital phenotypes (e.g., hypospadias) constitute a DSD (Vilain & Sandberg, 2009). With these caveats, the conditions subsumed under the umbrella term DSD are individually rare but, in the aggregate, have an estimated incidence of 0.1–0.5 % of live births (Arboleda et al., 2013).

Since the mid-1950s, clinical management of DSD has been guided by the "optimal gender policy" (Meyer-Bahlburg, 1998; Money, Hampson, & Hampson, 1955), according to which the gender assignment decision was based on the "best combined prognosis for good reproductive function (if attainable at all), good sexual function, minimal medical procedures, an overall gender-appropriate appearance, a stable gender identity, and a reasonably happy life" (Meyer-Bahlburg, 1998). Development of persons with DSD has also drawn the attention of researchers interested in the influence of atypical sex hormone exposure during steroid-sensitive periods of brain development (Berenbaum, Duck, & Bryk, 2000; Collaer & Hines, 1995; Hines, Brook, & Conway, 2004). This interest represents an extension, to humans, of animal experiments demonstrating that sex hormones present during sensitive periods of brain development are responsible for sex differences in behavior across a wide range of mammalian species (Hines, 2011). In this context, researchers adopted DSD as a model for testing hormonal hypotheses related to the influence of early androgen exposure on behaviors exhibiting sex-related variability in humans, in particular psychosexual differentiation (i.e., gender identity, gender role, and sexual orientation) and sex differences in neurocognitive function. This approach is nowhere more clearly illustrated than in the study of girls and women with congenital adrenal hyperplasia (CAH) resulting from 21-hydroxylase deficiency (Speiser & White, 2003).

In 21-hydroxylase deficiency CAH, the most common cause of DSD in persons with a 46,XX karyotype, excessive adrenal androgen biosynthesis results in masculinization of the genitals. A systematic review of studies (published between 1955 and 2009), examining psychological endpoints in persons with CAH, suggests an imbalance between theoretical interest in hormonal hypotheses of gender development and consideration of CAH-related experiences and contextual factors potentially influencing psychological outcomes in both affected women and men (Jordan-Young, 2012; Stout, Litvak, Robbins, & Sandberg, 2010).

In this chapter, we propose a third approach to the evaluation and clinical care delivered to patients affected with DSD and their families which encompasses the optimal gender policy and prenatal hormone perspectives. This "noncategorical" approach guides theory development and clinical care by taking into account a growing body of evidence that successful developmental trajectories of persons with chronic medical conditions are influenced as much by the psychosocial environment, supports, and organization of healthcare delivery as by the specific nature of the person's medical condition (Stein, 2011; Stein & Jessop, 1982). Such an approach holds the potential to systematically account for variability in DSD patient quality of life outcomes and lead to translating clinical interventions, proven effective in the management of other chronic conditions, to the circumstances faced by those affected by DSD.

5.2 The "Noncategorical" Approach

Major advances in therapeutics for specific pediatric conditions have strongly contributed to a disease-specific ("categorical") approach to care (Stein, 2011). In the case of DSD, this approach has contributed to a better understanding of genetic factors responsible for DSD and progress in genital surgical techniques. A categorical approach applied to DSD has also been associated with an emphasis on the process of psychosexual differentiation (Hines, 2011; Meyer-Bahlburg, 2008).

In comparison to knowledge about psychosexual development, we face major gaps in our understanding of other factors likely contributing to specific and global adaptation in persons with DSD. At this time, we have little more than speculation to account for variability in health-related quality of life (HRQoL) outcomes (in the relatively rare case in which quality of life is measured). To date, there has been little reliance on theory or research strategies derived from developmental psychology (typical and atypical) or pediatric psychology that considers the interaction of biological and environmental factors (Pickles & Hill, 2006; Rose, Holmbeck, Coakley, & Franks, 2004; Wallander, Thompson, Alriksson-Schmidt, & Roberts, 2003). Such approaches routinely consider risk and protective factors and cognitive appraisal and coping processes that are critical for testing competing theories about developmental pathways. A broadened clinical and research agenda is warranted, in part, to respond to justifiable criticism by former patients and advocates that poor psychosocial or psychosexual outcomes may be less a function of atypical sex hormone exposure or surgical procedures than the consequence of a complex interaction among experiences (e.g., medical/surgical decision-making, experience of DSD as stigmatizing and associated with feelings of secrecy and shame, financial hardships attendant with a chronic medical condition, mental health or marital problems that predate the child's birth) that modulate outcomes within and across developmental stages.

A noncategorical approach takes into account the unique aspects of the child's medical condition while also considering the total life experience of the child, family, and broader social context. According to this view, children and families face common challenges, regardless of the type of chronic pediatric condition (e.g., diabetes, asthma, DSD), and that adjustment and coping are influenced as much by the social environment as by the specific medical condition (Stein, 2011).

The noncategorical approach emphasizes the commonalities in life experiences and the burdens shared across diverse chronic medical conditions. For example, the disability-stress-coping model (Wallander et al., 2003) has demonstrated substantial heuristic value in pediatric psychology. Similarly, psychological approaches found to be effective in the management of other chronic conditions will potentially have utility when adapted to DSD. One of the more controversial topics in DSD care concerns the risks versus benefits of educating the affected person about their condition and its prognosis. In this context, the DSD consensus statement noted the proven value for positive psychological adjustment of openness as learned from very different conditions and circumstances, including pediatric HIV (American Academy of Pediatrics, 1999), cancer (Chesler, Paris, & Barbarin, 1986), and adoption (Schor, 1999).

The Consensus Statement implicitly acknowledges the importance of noncategorical factors when it balances the significance of accurate diagnosis and optimal surgery with details of *how* care is delivered and expands the range of outcomes to be tracked (Lee et al., 2006). A noncategorical approach to pediatric chronic conditions is predicated on sensitivity to the family's psychosocial environment, including supports and organization of healthcare delivery.

5.3 The DSD Team

5.3.1 Team Structure and Function

The Consensus Statement stresses that "optimal care for children with a DSD requires an experienced *multidisciplinary* team" (italics added) (Lee et al., 2006). The team consists of pediatric subspecialists in neonatology, endocrinology, urology (and surgery), gynecology, genetics and genetic counseling, psychology/psychiatry, social work, and bioethics. To this list, we add child life specialists who promote effective coping, particularly in response to healthcare procedures and hospitalization, through play, preparation, education, and self-expressive activities. They provide emotional support for families (including siblings) and encourage optimum development of children facing a broad range of challenging experiences in the medical setting (Wolfer, Gaynard, Goldberger, Laidley, & Thompson, 1988). Not all of these specialists are needed in every case: team composition will vary depending on the DSD diagnosis and individual child and family needs. Finally, the Consensus Statement emphasizes the importance of ongoing communication with the family's primary care physician who plays an important role in ensuring that comprehensive care remains coordinated (Council on Children with Disabilities, 2005).

A core principle of DSD care is to operate in a patient- and family-centered manner. Ascertainment of DSD, whether prenatally, in the neonatal period, or later, is commonly associated with high stress and limited information. Under these circumstances, parents struggle to absorb unfamiliar and highly complex concepts; they often do not perceive that treatment choices exist (Crissman et al., 2011). Many incorrectly assume that a particular diagnosis or phenotype implies a specific and immediate treatment, even though that treatment may not be "medically necessary" at the time or there may be alternatives to that approach. Decisions made under such circumstances can be associated with regret. Accordingly, the DSD team is responsible for educating parents (and, when older, the patient) to ensure that decisions are well informed, a prerequisite for informed consent.

The Consensus Statement describes the DSD healthcare team as "multidisciplinary." The terms "multidisciplinary" and "interdisciplinary" are often used interchangeably; however, meaningful distinctions need to be emphasized. Although a multidisciplinary approach ensures that the assessment and recommendations are comprehensive, this approach does not guarantee that the team is functioning synergistically or harmoniously (Pless, 1995). In fact, the "team" described in the Consensus Statement is more accurately characterized as "interdisciplinary" rather than "multidisciplinary." A multidisciplinary team approach is discipline oriented, with all providers working in parallel and with clear role definitions, specified tasks, and hierarchical lines of authority. In contrast, providers on an interdisciplinary team meet regularly in order to discuss and collaboratively set treatment goals for the patients and jointly carry out the treatment plans. Ideally, they are on the same hierarchical level and with a high degree of communication and cooperation among the team members. A by-product of this model is that team members learn how the goals of their own discipline may require modulation when taking into account considerations of the other specialties and the agreed-upon goal for the patient (Health Canada, 2004).

It possibly goes without saying, but success in the proposed healthcare delivery model depends on the depth of knowledge and experience of all specialists on the DSD team. Each member of the team is responsible not only for educating the patient and family about their specialty's contribution to overall care, but such communications must be informed by a working knowledge of the other specialties involved. "Success" for the patient cannot be defined according to the parameters of a single subspecialty. Instead, a common vision for success must emerge out of discussions among team members with essential involvement of the family.

5.3.2 Role of the Coordinator

The team can only function effectively as a unit if all members adopt the concept of the “interdisciplinary team” as described above and are willing to hold one another accountable as a team member (Sharp, 1995). To ensure such a process is respected and refined, a team coordinator is invaluable. The coordinator’s role is to (1) ensure that all specialists with a need to be involved are assembled at the earliest to review information available; (2) explain to the family (and when old enough to understand, the affected person) the concept of the team, the providers who will be involved in their child’s care, and their respective roles; and (3), based on a thorough evaluation, convene the team as necessary to arrive at a consensus regarding recommendations for immediate-, short-, and long-term care. Regular face-to-face communication among team members ensures continuity of health care which, in turn, increases the chance of optimal care for the patient and family (Mazur, 1983).

The role of team coordinator can be fulfilled by any of the specialists or someone added to the team specifically to fulfill that role. Team members well suited to this role include psychologists, genetic counselors, or nurses with the requisite communication skills. Key to accomplishing the responsibilities of the coordinator is adequate flexibility in the person’s schedule to coordinate the providers and serve as the liaison between the team and the family.

The team is obliged to maintain regular communication with the child’s primary care physician (i.e., the “medical home” [American Academy of Pediatrics & Medical Home Initiatives for Children With Special Needs Project Advisory Committee, 2002; Council on Children with Disabilities, 2005]), who represents an extension of the DSD team. It remains the responsibility of the generalist (pediatrician or family physician) to guarantee that care remains continuous, comprehensive, family centered, coordinated, and culturally effective. The primary care physician should be known to the child and family and should be able to develop a partnership of mutual responsibility and trust with them (American Academy of Pediatrics & Medical Home Initiatives for Children With Special Needs Project Advisory Committee, 2002). Historically, patients with DSD have not remained engaged or systematically followed by specialists from the time of diagnosis through transition to adult care. The medical home provides a safeguard against the risk of the patient and family becoming “lost” for follow-up or that issues not covered through DSD specialty care “slip through the cracks.”

5.4 Evaluation

It is safe to assume that families are not expecting to meet a behavioral health provider in the context of the initial DSD evaluation because first actions are usually medical: ruling out a life-threatening metabolic disorder, establishing a detailed description of the internal and external sexual reproductive structures, arriving at a diagnosis (biochemical and genetic), and delineating the range of surgical or hormonal options. Attention to medical and surgical factors is necessary for thorough evaluation and care but, unless balanced with consideration to the child's projected quality of life, may result in healthcare providers declaring success and the patient experiencing failure. As one expert remarked:

> All of these issues of functional potential [referring to scars from surgery, variation in gender-role behavior, prospects for romance, sexuality, marriage, parenthood] are more important to the average developing person with a DSD than the details of the molecular structure of genes, the variants of hormone synthesis, receptor defects, enzyme abnormalities, and the organization and activation of neural networks… (Meyer-Bahlburg, 2008).

This is why the behavioral health component is integral to clinical management of persons with DSD and their families (Lee et al., 2006). To deliver on its promise to provide holistic care that includes anticipating problems or barriers to care (medical and developmental), it is vital that a representative of the DSD team educates families about the structure and function of the DSD team (including a description of the specialties represented and their roles) when contact is first made. Particular emphasis needs to be placed on the nonhierarchical and fully integrated structure of the team to eliminate perceptions of stigma commonly associated with behavioral/mental health in other contexts. Such education includes the message that all team members view this component as essential in all cases. If individual members of the team are uncertain about the value of this component, a message of ambivalence may be subtly relayed to the family. Integrating behavioral/mental health services within the context of medical care increases the acceptability and openness to such services (World Health Organization, 2007).

This integrated behavioral health approach diverges from the traditional role of mental health provider as consultant who is called upon only when psychiatric problems are suspected. The focus of integrated behavioral health services is on anticipating and managing predictable challenges based on DSD-specific clinical research as well as studies of other chronic pediatric health conditions that a noncategorical approach would suggest are relevant. Thus, just as various other members of the team must first perform an evaluation, so too must the behavioral health provider. The emphasis here is on identifying factors that may act as barriers to positive psychological adjustment of the child and family, including nonspecific stresses associated with caring for a child with a chronic medical condition (e.g., travel and financial barriers to regular doctor visits, inadequate health insurance to cover costs of care). An additional and equally important goal of psychosocial assessment is to identify strengths of the individual and family that can be called upon to cope with a difficult, immediate, and chronic condition.

The following sections outline standardized tools appropriate for assessment in DSD and direct the reader to databases that summarize other assessment instruments. Following the distinction between categorical and noncategorical approaches described above, the assessment tools are similarly categorized, those that have been applied to address syndrome-specific aspects of DSD (i.e., concerns over gender-atypical development or gender dysphoria), followed by suggestions for assessment tools that capture crosscutting issues and experiences associated with a chronic medical condition.

5.4.1 Assessment of Psychosexual Differentiation

Gender identity, gender role, and sexual orientation comprise psychosexual differentiation. “Gender identity” refers to the person’s conviction of self as girl/woman, boy/man, or other. “Gender role” applies to behaviors that differ in frequency or level between males and females in a given culture and historical period and are seen as stereotypic for that respective gender. For example, career choices of women and men continue to exhibit significant sex-related variation, although secular changes in particular fields have been pronounced (Blau, Brummund, & Liu, 2012). “Sexual orientation” refers to sexual arousal to individuals of the same sex (homosexual), opposite sex (heterosexual), or both sexes (bisexual). A comprehensive review has been published of assessment methods, categorized by proband age, measure of gender identity, gender role (children, adolescents, and adults), and sexual orientation (adults only) (Zucker, 2005). The review also includes tables listing mode of assessment (e.g., questionnaires, tests, observation), informant (parent, child/adolescent, or adult), administration time, and effect size calculations used to gauge gender differences in the general population or for the purpose of proband-control comparisons.

5.4.2 Noncategorical Approach to Assessment

The noncategorical approach assesses domains that are not unique to persons with a DSD and their families, but are relevant to all children and adolescents with and without a chronic medical condition. A recent systematic review (Bradford & Rickwood, 2012) of psychosocial assessments employed in various (including medical) settings and used by multidisciplinary teams for individuals between the ages of 12 and 20 suggests that (1) self-administered questionnaires identified higher rates of risk behaviors than interviewer-administered questionnaires, (2) evidence is mixed as to whether paper-and-pencil administration produces more openness than computer-assisted administration, and (3) psychosocial assessment instruments can improve the rates of disclosure and enhance engagement between young people and healthcare providers.

The review identified 31 psychosocial instruments assessing 43 domains. The number of domains assessed by individual instruments ranged from 3 to 16. The most common domains addressed were social relations, education/work, mental health, physical health, emotional distress, harm or violence to self or others, and sexuality. Selected examples of other domains included presenting problem, spirituality/religion, personality, self-esteem, material well-being/financial status, home environment, and place in the community.

For those working with DSD patients, assessing parental stress, coping, and general family support (including financial resources) is important. The Psychosocial Assessment Tool (PAT), developed out of the Pediatric Psychosocial Preventative Health Model framework (Pai et al., 2008), was designed to screen for psychosocial risk in families of children newly diagnosed with cancer (Nielsen-Bohlman, 2004). With minor modifications, it has been modified for use in DSD by the first author.

Theory and research pertaining to pediatric chronic medical conditions can be used to guide the selection of constructs to be assessed, the methods and measures employed, and the manner in which the iterative assessment process is used to detect both risk and strengths that are used to guide counseling for both the affected person and the family (Rose et al., 2004; Zucker, 2005). As in the case of measures used to assess psychosexual differentiation, the tools selected to evaluate the status of all other domains should meet the highest psychometric standards. Today, there are readily accessible databases of high-quality measures available to tap many constructs of interest. The Patient-Reported Outcome and Quality of Life Instruments Database (PROQOLID; http://www.proqolid.org) was initiated by a nonprofit organization interested in promoting the appropriate use of patient-reported outcome measures by providing overviews of existing instruments, information on the availability of translations, and copyright information and facilitating access to these instruments and their developers. The National Institutes of Health has sponsored PROMIS® (Patient Reported Outcomes Measurement Information System; http://www.nihpromis.org), which is a database of psychometrically robust measures of patient-reported health status for physical, mental, and social well-being. PROMIS® tools can be used in research and to guide clinical care across a wide variety of chronic diseases and conditions and in the general population. Each set of questions tapping a particular construct have been extensively normed in the US general population and multiple disease populations. This feature makes it possible for the clinician to benchmark the adaptation of the DSD-affected person (child or adolescent) as well as the key caregivers in their lives.

The preventive approach implied by integrating behavioral health within the DSD team involves periodically assessing key individual and family functioning domains. The assessment also includes evaluating patient/family understanding of the DSD, the rationale for hormone replacement (as indicated), adherence to medical regimens, the patient's emerging body and self-image, degree of active engagement in medical self-care, and comfort in sharing information with select others, including peers and romantic partners. The optimal schedule for these assessments is not prescribed—although the patient and family should be informed early in their engagement with the team that the psychosocial evaluations will be repeated just as standard lab tests are repeated to inform ongoing care. Ideally, after the initial medical and psychosocial assessments are completed, families are given a summary of the overall plan for medical and psychosocial assessments as well as the possible interventions to be considered in both the short term and in the years ahead.

Upon entry to school, academic and peer relations in the school setting should be assessed and reassessed at major transitions, i.e., preschool to elementary, middle school to high school. Among DSD, Turner syndrome and Klinefelter syndrome, in particular (both examples of sex chromosome DSD), are recognized as associated with neurocognitive deficits.

A final note is warranted regarding the use of psychosocial tools in ongoing clinical care. The best instruments will be those that stimulate discussions between parents (and, when older, patients) and providers. A substantial research literature in DSD demonstrates how questionnaires and interviews are analyzed, in the aggregate, to create what is hopefully generalizable knowledge about these conditions. There are far fewer examples of how such tools figure into usual care, similar to how the results of biochemical tests are used to guide medical care. The litmus test for administering questionnaires in the clinical context is, first and foremost, whether the information obtained is potentially actionable. Identifying problems via parent or patient report on assessment tools which are then ignored by the clinician is to be diligently avoided. This circumstance has been identified as a factor significantly reducing the likelihood of a young person seeking future help (Rickwood et al., 2005). Of course, analyzing findings from these same instruments, across patients (i.e., in the aggregate) as part of clinical research approved by a local institutional review board, is not incompatible with the requirement that their selection be guided by the principle of clinical primacy.

5.5 Treatment

Once the medical facts regarding a patient's DSD are known (to the degree they can be known) and effectively communicated to the parents (including the fact that DSD are not, in general, life limiting), a number of shared issues and decisions come to the fore. One of the first may be the decision regarding gender assignment. Examples of other decisions concern the balance between secrecy and sharing of details regarding the condition and its implications (who should be told, when should the information be given, who should deliver it, and how best to do it), timing of various medical/surgical interventions and whether or not they are warranted at all, and managing parental emotions related to unlikely fertility of their child. Eventually, responsibility for treatment decisions and adherence to medical recommendations shifts to the child as he or she matures and becomes personally engaged in his or her care (Rapoff, 2010).

The salience of each psychosocial theme to be addressed waxes and wanes according to the child's developmental stage, but rarely completely disappears. The process (and not a single event) of educating the parents and the affected person requires a flexible, individualized approach of medical education and counseling that gradually increases in complexity and takes into account health literacy (Committee on Health Literacy, 2004) and emotional readiness. It also fosters open communication between parents and child as a high priority (Meyer-Bahlburg, 2004; Money, 1994). This iterative process should be explained and planned with the parents from the time of diagnosis (Carmichael & Ransley, 2002).

To facilitate patient- and family-centered care, the team ideally will provide the family with a document summarizing (1) facts about the medical condition, (2) possible medication regimen, (3) recommended schedule for periodic medical and psychological follow-up, (4) decisions to be considered now and in future years, (5) contact information for all DSD team members, and (6) support organizations for families affected by DSD. Such a document can relieve stress by offering a road map beyond the exigencies of the initial diagnostic period and increase confidence and trust that the team and support organizations will remain a resource to the family over time.

The goal of this entire process is to encourage the best quality of life for the child by bolstering the family's (and the affected person's) adaptive coping to stressors commonly associated with DSD and its management in much the same way that pediatric psychologists proactively assist families in coping with other chronic pediatric conditions. This approach is based upon, and guided by, information obtained in the psychosocial assessment conducted in conjunction with the medical evaluation. Below are selected issues, identified by providers, parents of a DSD child, and affected persons with a DSD, that require special attention by the DSD team.

(a) *Decision-making in DSD*. Barriers to parents' active participation in the decision-making process include (1) uncertainty in the medical community regarding "best practices" in the diagnosis, medical/surgical management, and strategies for optimal psychosocial management (Berenbaum, 2006; Sandberg, Gardner, & Cohen-Kettenis, 2012); (2) shared perception by parents and health-care providers that the birth of a child with unclear sex constitutes a "psychosocial emergency" (Chase, 1998; Hiort, Thyen, & Holterhus, 2005; Meyer-Bahlburg & Blizzard, 2004; Stein, Sandberg, Mazur, Eugster, & Daaboul, 2003) requiring immediate action, despite the fact that surgical procedures performed on the genitalia of newborns or infants to modify appearance are elective rather than medically necessary (Frader et al., 2004; Gillam, Hewitt, & Warne, 2011; Karkazis, Tamar-Mattis, & Kon, 2010); (3) the experience of DSD as extremely rare and stigmatizing, resulting in parents neglecting support and resources that can come from extended family, friends, peer support organizations, and trusted physicians in the medical home; (4) the dearth of readily accessible information (from a health literacy perspective) for parents and other families that explains DSD in terms of well-understood biological principles guiding sex development (in contrast to the myths regarding "intersex" or "hermaphrodites") (Consortium on the Management of Disorders of Sex Development, 2006); (5) lack of rigorous methods for assessing patient (and in the case of young children, parent proxy) values and preferences relevant to DSD decision-making; and (6) parental emotional distress and fear of stigma-related social isolation interfering with cognitive processes necessary to balance the risks and benefits of treatment options for the child. Under these circumstances of high stress and limited information, parents struggle to absorb unfamiliar and highly complex concepts and often do not perceive that treatment choices exist (Crissman et al., 2011). Decisional regret would be an easily understood consequence of such circumstances.

Informed consent for procedures, medications, or other therapeutic interventions is predicated on parents (and when sufficiently mature, the affected person) being fully informed of potential risks and benefits. Nearly 20 years ago, the US federal government defined informed consent as "a process, not just a form" (Office for Human Research Protections [OHRP] & Office for Protection from Research Risks, 1993), highlighting the importance of thorough and meaningful informed consent. Yet research suggests that most decisions are not fully informed: pros and cons of a given treatment choice are typically not discussed, nor are alternatives (Gomes et al., 2012). Parents can only provide proxy permission for their child if they are provided with education that is accessible and repeated over time. To ensure that understanding is adequate, there should be repeated opportunities to ask questions. The coordinator is in a perfect situation to review the choices put before the family by members of the DSD team and to act as a "navigator" assisting them to align their choices with family values and preferences, a key element of shared decision-making.

(b) *Timing of procedures*. DSD, with few exceptions, do not require lifesaving medical interventions. One exception would be hormone replacement in persons with salt-wasting CAH. Consequently, whether or not to have a procedure performed, for example, genital surgery, when to have it (early or later), and what is a reasonable goal of the procedure (e.g., removal of testicular tissue in an infant with mixed gonadal dysgenesis reared female, but waiting until the child is old enough to decide for herself whether or not to reduce the size of her clitoris) are not decisions that need to be made immediately. Consequently, there is time to discuss all opinions and reflect on the potential benefits and risks of each. Informed decisions are predicated on such discussions.

(c) *Sharing information*. Educating children, adolescents with a DSD, and their families about the condition and its implications is a vital aspect of psychological management. It is important that they have a full understanding of the condition for only then can they understand the treatments the team offers and give fully informed consent to whether or not they agree to the treatments. The literature has termed this process "disclosure"—but this word has a negative connotation because it suggests that something hidden is now revealed. Furthermore, disclosure implies simply giving information without the process of interaction with patients as one would do in an educational setting. Therefore, we suggest "education" replace "disclosure." Evidence from adoptees and those with chronic medical conditions suggest that education can enhance psychological adaptation (Wiener, Mellins, Marhefka, & Battles, 2007). Such education is a long-term process that starts with the parents and eventually with the child when adequately mature and, finally, with the adult.

Beginning in the early teenage years, it is always important to ask patients "What do you know about why you are here today?" followed by "What do you know about your condition and treatment?" John Money (2002) pointed out that patients are questioned by their peers about missed school, special accommodations made (e.g., missing showers in school after gym class), or taking medications. Posing such questions as part of the longitudinal assessment provides the patient with the opportunity to rehearse answers and be coached, through role-play, if necessary. Competence in providing an explanation to peers regarding physical differences has been demonstrated to result in more positive impressions of the person by others (Edwards, Topolski, Kapp-Simon, Aspinall, & Patrick, 2011).

The provider must also be aware that siblings, often inadvertently overlooked, need explanations as to why their brother or sister is in the hospital, goes to the doctor frequently, or takes medication (Austin, Tamar-Mattis, Mazur, Henwood, & Rossi, 2011; Mazur, 1983). Finally, relatives and close friends may have a need to know; holistic care delivered by the team includes the skill building of parents on how to inform these individuals. Team members can also offer to assist families in educating individuals outside the circle of family and friends who have a need to know (e.g., teachers, childcare workers, baby sitters).

(d) *Genital examinations/medical photography*. Traditionally, persons with a DSD diagnosis were examined repeatedly in front of a number of physicians, many of whom were in training. They were photographed in the nude and pictures taken of their genitals. Such practices have negative and, often, severe psychological aftereffects (Creighton, Alderson, Brown, & Minto, 2002; Money & Lamacz, 1987). Fortunately, in the digital age, there are a number of avenues to train physicians which do not require direct observation of the patient. When the child requires a genital examination, consideration should be given to distraction techniques delivered by child life specialists or other qualified members of the team to reduce procedural anxiety. In a study of children (3–8 years old) receiving a genital examination, use of video glasses were found to be more effective than active (singing, blowing bubbles) or passive (being read to) play in reducing anxiety and improving satisfaction levels among children undergoing a genital examination (Berenson, Wiemann, & Rickert, 1998).

DSD are congenital and chronic conditions, akin to other medical conditions, which pose developmental challenges for affected individuals and their families. It is quality of life issues (e.g., “functional potential”) that are the focus of the average person and parents (Carmichael & Ransley, 2002). As mentioned in the preceding section, the ultimate question parents ask is “How is my child going to develop in all aspects of life?” We have limited evidence with which to answer this question. However, if we view their question in terms of developmental pathways, as has been suggested (Sandberg et al., 2012), then “the “pathway” metaphor can be as productive for studying the psychological development of persons with DSD as it has been in the much broader field of child development and developmental psychopathology.” This comparison also alerts us to follow patients throughout development so that we can learn how medical and surgical interventions may or may not influence individuals’ quality of life outcomes. To adopt this view means that patient (and family) care requires persistent attention to issues that are time sensitive (e.g., if or when to perform surgery; when and how to educate the child of different aspects of the DSD) and linked to developmental experiences and capacities. Medical education and counseling for children and their families is a continuing process of gradually increasing complexity that takes into account health literacy (Committee on Health Literacy, 2004) and emotional readiness.

Below, in outline form, are issues that emerge by developmental stage and which require attention by the DSD team. As noted above, the psychosocial evaluation requires a balance between the categorical (DSD-specific) (Zucker, 2005) and non-categorical (Bradford & Rickwood, 2012) aspects of development and adaptation. Additional details can be found in several reviews (Mazur, 1983; Meyer-Bahlburg, 2008; Sandberg et al., 2012).

- *Prenatal period*. Given sustained developments in medical technology, DSD are increasingly identified in utero and, therefore, clinical management can begin before the child is born. There is substantial variation in healthcare providers' knowledge regarding DSD. Because these conditions are individually rare and, historically, understudied and misunderstood, parents are at risk of receiving outdated or incomplete information unless major efforts are made in the context of interdisciplinary care teams.
- *Birth of an infant with a DSD*. The birth of a child with a DSD is stressful for parents and members of the healthcare team. The "right" decisions about gender assignment (is it a boy? a girl?) and the best course of action (should there be surgery? what kind? when?) are not obvious (Crissman et al., 2011; Fedele et al., 2010). There are a number of resources available to explain and to help parents visualize the process of sex development, both typical and atypical (AboutKidsHealth, 2012; Consortium on the Management of Disorders of Sex Development, 2006; Money, 1994).

  Through the efforts of the interdisciplinary team, in particular the team coordinator, parents are informed of all medical information available, as well as the limits of our knowledge, to eliminate any doubt that information is being withheld from them. A key goal of this process is to have the parents understand that the relationships between diagnosis and treatment are far from perfect; for example, a specific molecular diagnosis is compatible with different decisions, including gender assignment. Many parents will need help in accepting that decisions are legitimately based, in part, on their personal preferences, values, and cultural background.
- *Childhood*. The challenge here is to provide age-appropriate information that (1) provides a context for why there are visits to the doctors, in excess of their peers, and why they may be taking medication and (2) provides a template upon which age-appropriate information on their condition can be given and eventually repeated and added to in adolescence. Parents need to be prepared for the likelihood that gender-role behavior of the child may be atypical for gender of rearing but that this is not an indication of incorrect gender assignment. Proactive education about this aspect of the DSD can reduce stress and unnecessary worry.
- *Adolescence*. With adolescence comes greater cognitive awareness and questions about their condition, their psychosexual development with focus on intimacy, sexual functioning, fertility, and telling peers about their condition. Evaluation of

psychosexual status as well as general behavioral and emotional function (Bradford & Rickwood, 2012) is in order for the purpose of preventing problems and giving guidance. The goal is to have the adolescent completely knowledgeable about their DSD condition, comfortable with this knowledge so that (1) it does not act as a barrier to a positive quality of life and (2), as adults, they can educate physicians about their condition if necessary and participate actively in their own care.

The focus on quality of life (encompassing the domain of psychosexual development) obligates the healthcare team to be sensitive to the needs of parents and their child at any given time along the "pathway" and cognizant that decisions and timing of medical interventions may influence the individual's developmental trajectory. Such awareness necessitates periodic education and counseling around these issues if care is to be optimal.

5.6 Distinctions Between DSD and Transsexualism

"Gender dysphoria" refers to the subjective conflict between a person's gender identity and their gender assigned at birth based on their external genitalia. Gender dysphoria most commonly occurs in persons born with *typical* somatosexual development (see Chap. 3) but can occur among persons with DSD. There are several reasons, however, why gender dysphoria in these two groups should be distinguished. For example, gender-atypical behavior is a well-recognized behavioral feature of particular DSD syndromes (e.g., tomboyish behavior in girls with CAH), with considerable evidence to suggest that it is the consequence of the organizational effects of androgens on steroid-sensitive brain regions during sensitive (prenatal) periods of brain development (Berenbaum & Beltz, 2011; Hines, 2011). There is far less evidence to suggest a prenatal action of androgens on development of gender identity. Accordingly, the DSD consensus statement warns against viewing gender-atypical behavior as a forerunner of gender dysphoria (Lee et al., 2006). Gender dysphoria and gender change in persons with DSD vary dramatically according to DSD syndrome and gender assignment (de Vries, Doreleijers, & Cohen-Kettenis, 2007; Meyer-Bahlburg, 2005). For example, with very limited exceptions, patients with complete androgen insensitivity syndrome assigned as girls in infancy identify as girls/women. At the other end of the continuum of gender identity stability are the syndromes associated with errors in testosterone biosynthesis, such as 5-α-reductase-2 deficiency; in this specific syndrome, between 56 and 63 % of affected persons assigned as girls at birth change their gender, usually during adolescence or adulthood (Cohen-Kettenis, 2005).

While more complete explanations for gender dysphoria in persons with DSD and those without require further research, it is indisputable that those affected with DSD have experienced very different life events than persons without DSD. Suspicion of a DSD triggers a series of events that dramatically distinguish the experiences of those affected from those born physically typical. These events consign the affected person and parents, at least through infancy, childhood, and adolescence, to monitoring by healthcare providers, much like anyone with a chronic illness. For the individual born with ambiguous genitalia, or discordance between karyotype and genital phenotype, the question that immediately faces healthcare providers and parents is to which gender to assign the infant. The history may even include a change of the initial gender announcement, with parents having to re-announce the gender of their child to siblings, grandparents, and friends. There may also be an immediate necessity for lifesaving medication, as in the case of infants with CAH. There are also salient issues surrounding potential surgical reconstruction of the genitals, the possibility of contra-sexual pubertal development or hormone treatment to induce puberty, and general state of good health (i.e., continued hormone replacement to maintain physical health). Consequently, the context within which a child with DSD grows and develops is much different from that of a child without a DSD. The extent to which these experiences contribute to gender dysphoria in a subset of patients with DSD remains unclear and understudied.

Failure to differentiate between persons with and without a clearly defined DSD may hamper studies of etiology and optimal clinical management. Persons with a DSD diverge from persons with gender dysphoria who were born physically typical in terms of age of onset, prevalence, sex ratio, and, perhaps most importantly, awareness and understanding of their DSD (Mazur, Colsman, & Sandberg, 2007; Meyer-Bahlburg, 1994; Richter-Appelt & Sandberg, 2010). Such persons may be at risk for misunderstanding their complex medical history. Therefore, a central difference between assessing a person with gender dysphoria who also has a DSD diagnosis and one who does not is in discerning to what degree the presenting gender problem is associated with possible confusion or lack of information about the DSD. Such an assessment requires that the clinician understand what is known etiologically about DSD and involves providing information to the person about their DSD in language they can understand. It also means that the provider must know what behavioral and cognitive concerns are associated with the particular DSD as well as concerns that are crosscutting (e.g., all DSD involve the sexual/reproductive anatomy or function).

The forthcoming DSM-5 introduces the term gender dysphoria to replace the current gender identity disorder of the DSM-IV-TR. In the proposed change, there are two subtypes: with and without a DSD. Also, the term “sex” has been replaced by “assigned gender” in order to make the DSM-5 criteria applicable to persons with DSD.

5.7 The Disorders of Sex Development: Translational Research Network (DSD-TRN)

Beginning in late 2011, the National Institute of Child Health and Human Development (of the National Institutes of Health) initiated support for a patient registry-based platform for hypothesis-driven research on the mechanisms of sex development and evidence-based care for patients and families affected by DSD. Specific network aims include identifying novel genetic mechanisms involved in sex development and an improved understanding of DSD pathophysiology, standardizing the process of genetic and biochemical diagnosis and anatomic descriptions of DSD phenotypes, and establishing a comprehensive psychosocial assessment battery suitable for use in routine clinical care—a necessary step leading to evidence-based psychosocial treatment protocols. The assessment battery targets both syndrome-specific and non-categorical aspects of DSD; only tools expected to yield information of immediate value to ongoing care are included. For example, the Psychosocial Assessment Tool (see Sect. 5.4 for assessment tools), a tool originally designed for families of newly diagnosed children with cancer, is among the earliest instruments to be administered in the DSD-TRN to screen for psychosocial risk in families.

The assessment protocol is evolving both in terms of the measures incorporated and the process for their administration, interpretation, and follow-up care taking into account the variability in team structure across participating sites. The DSD-TRN is a learning collaborative that is generating quality improvement in the process of DSD care across variable healthcare delivery environments; as such, the lessons learned are more likely to be transferable to additional DSD teams outside of the current research network.

5.8 Barriers to Implementing the Integrated Model of Care

The Consensus Statement calls for care to be delivered by integrated teams that include integration of behavioral health providers. However, there is a dearth of behavioral specialists qualified to join such interdisciplinary teams, and funding for such positions remains a far lower priority than introduction of new medical technologies and procedures. Furthermore, there are no enforcement mechanisms behind consensus statements, and it is left to the discretion of medical institutions, local providers, and payers of services to determine how health care will be delivered. Accordingly, examples of interdisciplinary teams, including fully integrated behavioral health care, are very limited.

Perhaps the greatest barrier to implementation of the holistic model of care proposed here is the dynamics of teams, in general. True teamwork is a rarity whether in academia, medicine, or sports. The effort required creating the structure and function of a DSD team described in Sect. 5.3 is enormous. Time spent in coordinating care goes uncompensated and each specialist on the team has clinical and administrative responsibilities that pull him or her away. Even more daunting than the logistical and financial considerations are the common "dysfunctions" of teams. Lencioni (2002) summarized the five dysfunctions to productive teamwork as (1) absence of trust, (2) fear of conflict, (3) lack of commitment, (4) avoidance of accountability, and (5) inattention to results. Although Lencioni's and related books are ostensibly focused on leadership in the business community, the pitfalls described are universal and, arguably, the greatest challenge to creating a model of care in DSD that is, at its core, patient and family centered.

5.9 Conclusions

The stark contrast between the proposed model of care and the realities of behavioral health services, internationally, might evoke cynicism in the reader. Recognizing that the US healthcare system does not provide consistent, high-quality medical care to all people, the Institute of Medicine, in 2001, issued a report titled *Crossing the Quality Chasm: A New Health System for the 21st Century* (Institute of Medicine and Committee on Quality of Health Care in America, 2001). The report focused on fostering innovation and improving the quality of care. Adherence to the principles of patient- and family-centered care was emphasized, including respect for patients' values, preferences, and expressed needs; coordination and integration of care across boundaries of the system; providing information, communication, and education that people need and want; and guaranteeing physical comfort, emotional support, and the involvement of family and friends.

What factors are likely to change the status quo? Certainly, the staggering costs of health care without accompanying improvements in the quality of outcomes will drive change. Another influence which holds substantial promise would be the development of partnerships between providers, researchers, and families affected by DSD. The example of the Cystic Fibrosis Foundation (CFF) comes to mind in this context. This US nonprofit organization, neither a provider nor payer of healthcare services, awards grants for research, supports clinical trials, and accredits specialized centers for patient care. In addition, for over 40 years, the CFF has managed a patient registry to track health outcomes and provide data for quality improvement in the delivery of care (Gawande, 2004). Might an organization, outside of health care, deliver improvements in the quality of care in DSD following the success of the CFF? In closing, the stage is set for improvements in the health-related quality of life outcomes of persons with DSD and their families. We predict that these improvements will accompany a shift in focus from "what" to "how" we deliver care.

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Chapter 6
Psychosexual Development in Individuals with Disorders of Sex Development

Birgit Köhler, Martina Jürgensen, Eva Kleinemeier, and Ute Thyen

Abstract Disorders of sex development include a large, very heterogeneous group of genetic conditions resulting in atypical anatomical development of the sex organs due to errors in genes determining fetal gonadal development, hormone production, or response to hormones. Broad categories encompass individuals with 46,XY karyotype and varying degrees of undervirilization who may live as boys or girls, may live as men or women, or may choose a third or no gender as adults. Individuals with 46,XX karyotype are mostly women affected by prenatal excess androgen exposure with varying degrees of virilization. In Europe, the great majority of 46,XX DSD persons live in the female gender, which may be different in other cultures and healthcare systems where hormone treatment may be late or not available. Among many outcomes, psychosexual development can be affected by the condition itself, medical interventions such as surgery or hormone replacement therapy, impact of delayed or precocious development, experience of stigmatization or psychological trauma, societal expectations of gender role behavior, dysphoria with assigned sex of rearing, and comorbid mental health conditions. In this chapter, we review the literature and present the major findings of the German clinical evaluation

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study which included about 400 individuals with DSD of all ages. The conclusions follow the findings and the considerations of the National German Ethical Board issued in 2012.

6.1 Introduction

The psychosexual development of the child into an adolescent and an adult is a complex process with biological and anthropological determinants and takes place in social and cultural contexts. Various constructs of psychosexual development can be distinguished: gender identity, gender role behavior, and sexual orientation (Maccoby, 1988, 1998; Martin, Ruble, & Szkrybalo, 2002). Gender identity is understood as the fundamental feelings of being either male or female, whereas gender role behavior includes behavioral manner, attitude, and personality characteristics, which are seen as gender typical in relation to cultural and historical background (Leaper, 2011). Sexual orientation is defined by those to whom people are drawn erotically and sexually. All three aspects demonstrate great variability within gender groups. In addition to these three constructs of psychosexual development, other central aspects of sexual development are sexual experiences and contentedness with sexuality. In particular, the building of a satisfying sexuality is seen as essential for personality and identity development (Impett & Tolman, 2006).

In humans, the typical development into a girl or boy from an embryo with an undifferentiated gonad anlage is a complex, genetically programmed process. Girls generally have a chromosomal complement with sex chromosomes XX, boys having XY. During embryonic development, the processes of sex determination, i.e., the establishment of gonadal gender, and sexual differentiation (the construction of the inner and outer genitalia) are separate processes. These processes are directed by genes and in succession by hormones, which can be interrupted, hindered, or modified by a multiplicity of influences, resulting in atypical development (Hughes, Houk, Ahmed, Lee, & LWPES/ESPE Consensus Group, 2006). These atypical developmental paths are described as “disorders” in the field of health research, which is meant as a value-free description of a departure from typical development. Whether and to what extent these result in impairments in health and well-being depends importantly on positive and negative environmental influences. However, in some cases of atypical development, health aspects, in addition to psychosexual development, are affected, leading to the requirement of long-term or lifelong medical treatment.

Disorders of sex development (DSD) cover a heterogeneous set of congenital deviations of sex determination and differentiation. We distinguish between 46,XX karyotype DSD with androgen excess, 46,XY DSD with androgen deficit, and sex chromosome DSD. The most prominent examples for the first are congenital adrenal hyperplasia (CAH) and, in the latter, androgen insensitivity syndrome (AIS) (Hughes et al., 2012). Gender assignment, the development of gender identity, atypical gender role behavior, sexual orientation, and satisfaction with own sexuality for people with DSD are the subjects of clinical studies, as well as academic and public debate. Because of biologically atypical gender development, dissatisfaction with the allocated sex of rearing cannot be classified as gender identity disorder. People with DSD who feel dissatisfied with their social gender are not displaying a disorder of gender identity but rather a discrepancy between the gender identity they experience and sex of rearing which is often chosen by their parents. On these grounds, uncertainty relating to sex of rearing has in recent years been described as gender dysphoria, which can express itself as unease with one's own gender, as well as a rejection of the sex of rearing (Cohen-Kettenis, 2010).

In many DSD studies, the constructs of gender dysphoria, gender role behavior, and sexual orientation are used as outcome measures, without being clearly defined and being confused with one another (de Vries, Doreleijers, & Cohen-Kettenis, 2007). This restricts the validity of the results: Whereas gender identity disorders in individuals without DSD and gender dysphoria in people with DSD are psychopathologically significant, gender-atypical role behavior and nonheterosexual orientation are cases of behavior which do not necessarily result in individual suffering. Correspondingly, gender-atypical behavior and homosexual orientation are not criteria for impairment in psychosexual development in people with DSD. Furthermore, theoretical interest in the role of prenatal androgens in shaping psychosexual differentiation has led to a focus on psychosexual outcomes in the majority of studies investigating the well-being and adaptation of people with DSD. Stout, Litvak, Robbins, and Sandberg (2010) state that a broader conceptual model should include "…the role of other potential factors in mediating or moderating the influence of (CAH) pathophysiology on psychological outcomes in both affected females and males. The latter approach offers to identify factors amenable to clinical intervention that enhance both health and quality of life outcomes in CAH as well as other disorders of sex development." The authors suggest, considering experience with sexuality, the impact of hormonal dysregulation, body image, surgery, and psychological trauma on mental well-being as well as social relationships, both as end points and as determinants of psychological well-being. While health-related quality of life is accepted as a very important patient-reported outcome, researchers must also take into account specific aspects related to the condition (Wisniewski & Mazur, 2009). While we generally agree, this review will again focus on psychosexual development in individuals with DSD. We believe that these outcomes are most relevant to the population and must be better understood to build theoretical models about the relationship of factors determining quality of life and participation in society.

6.2 Psychosexual Development in Children, Adolescents, and Adults: Overview

Psychosexual development in children with DSD is marked by unusual pre- and postnatal hormonal effects, as well as the typical biological, psychological, and social influences. These can be expressed through an excess of gender-atypical hormones or a deficit of gender-typical hormones, e.g., prenatal androgen effects in a female phenotype (resulting in masculinized genitalia) and female gender assignment or clearly decreased androgen effects (resulting in undervirilized genitalia) in male gender assignment. Developmental stages can occur prematurely, such as with the early formation of secondary sexual characteristics (e.g., in children with congenital adrenal hyperplasia) or too late (e.g., in androgen insensitivity syndrome), or show phenotypically unusual features (e.g., virilization in a girl with 5α-reductase deficiency).

A certain consensus exists that high prenatal androgen effects in girls and women with DSD (e.g., CAH, PAIS, mixed gonadal dysgenesis) lead to more boy-typical gender role behaviors (Auyeung et al., 2009; Berenbaum & Snyder, 1995; Hall et al., 2004; Hines, 2006; Hines, Brook, & Conway, 2004; Jürgensen et al., 2010). As a rule, in spite of their increased "tomboy" behavior, these girls develop a female gender identity (Berenbaum & Bailey, 2003; Meyer-Bahlburg et al., 2004). The literature, however, contains evidence of a raised risk of gender dysphoria in these children (Dessens, Slijper, & Drop, 2005; Slijper, Drop, Molenaar, & de Muinck Keizer-Schrama, 1998). A recent literature review nonetheless concluded that extremely virilized 46,XX CAH patients who were reared male with healthy social support may enjoy satisfactory levels of social and sexual function as male adults (Lee & Houk, 2010). This finding stresses the importance of the social and cultural environment.

On the other hand, markedly feminine behavior in XY girls and women without androgen effects (i.e., girls and women with 46,XY DSD, such as complete androgen insensitivity syndrome) has been repeatedly described. These children show both clear girl-typical behaviors and the development of a clearly female gender identity with no suggestion of gender dysphoria (Cheikhelard et al., 2008; Hines, Ahmed, & Hughes, 2003; Jürgensen et al., 2007).

Referring to gender identity in children with DSD, the initial sex of rearing is a good predictor for later gender identity. It is important, however, to distinguish between the various diagnoses. Prepubescent and pubescent girls and women with CAH show no signs of gender dysphoria or gender change (Arlt & Krone, 2007). Only occasional studies reveal signs of gender dysphoria or gender change in this subgroup (Dessens et al., 2005; Warne et al., 2005).

Gender change is not as rare in girls and women with the 46,XY karyotype and androgen effects (Praveen et al., 2008; Reiner, 2005). Individuals with 17β-HSD deficit or a 5α-reductase deficiency are usually raised as girls and are more likely, among all DSD cases, to later request a sex change (Cohen-Kettenis, 2005; Praveen et al., 2008). Children and adolescents with genital malformation (e.g., agenesis of the penis, cloacal exstrophy) who grow up as girls and had a normal level of male hormones at birth also have a raised rate of sex change from the female to the male sex role (Meyer-Bahlburg, 2005). Contrary to this, no evidence of gender dysphoria is found in boys and men with DSD and atypically low androgen effects, i.e., boys and men with partial androgen insensitivity syndrome or mixed gonadal dysgenesis (Reiner, 2005; Szarras-Czapnik, Lew-Starowicz, & Zucker, 2007).

Although the theme of *sexuality and body image* is considered a central one for adolescents with DSD, there was no systematic research in this field for a long time.

Most research focused on DSD-related disorders in sexual function and anxiety in adults. Adolescents with DSD were believed to be more reticent to develop love and sexual relationships (Cohen-Kettenis & Pfaefflin, 2003). Studies of adolescents with hypospadias (abnormally placed opening of urethra) and genital malformation show that these young people fall in love later and have a fear of the reactions of potential sexual partners and, because of this, they are more likely to develop emotional problems (Ebert, Scheuering, Schott, & Roesch, 2005; Mondaini et al., 2002; Reiner, Gearhart, & Jeffs, 1999; Schönbucher, Weber, & Landolt, 2008). Multiple or late operations, as well as severe forms of hypospadias, can have a negative influence on sexual development (Schönbucher et al., 2008).

Studies of adults with DSD frequently return to the question of whether the DSD-related genital operations affect sexual function and the level of satisfaction with sexuality. Disorders in sexual function, anxiety, and sex avoidance behavior are frequently described (Crouch, Liao, Woodhouse, Conway, & Creighton, 2008; Frisén et al., 2009; Gastaud et al., 2007; Wang et al., 2009; Warne, 2008; Warne et al., 2005).

The first study in Germany of the quality of life and sexual life of adult women with CAH was performed in the 1990s. The study showed no difference in partnership and satisfaction with overall sex life in women with CAH compared to controls (Kuhnle & Bullinger, 1997; Kuhnle, Bullinger, Schwarz, & Knorr, 1993). Later studies showed a preference for "male" interests and professions and also a high proportion of homosexuality (Frisén et al., 2009; Meyer-Bahlburg, Dolezal, Baker, & New, 2008). Several studies have investigated sexual function and the quality of sexual life from childhood to puberty in women with CAH following genital surgery with clitoroplasty and vaginoplasty. An English study reported poor cosmetic and functional outcome of genital surgery with decreased clitoral sensibility, vaginal stenosis, and problems with orgasm (Creighton, Minto, & Steele, 2001). Subsequently, different European studies reported vaginal stenosis (10–36 %), some impairment of clitoral function, and considerable impairment of sexual life including orgasm in women with CAH, following surgery (Gastaud et al., 2007; Nordenskjöld et al., 2008; Stikkelbroeck et al., 2003). Absence of sexual activity is higher in women with CAH and might be due to the fear of looking different or doubts about the practicability of sexual intercourse (37–50 %) (Frisén et al., 2009; Krege, Walz, Hauffa, Körner, & Rubben, 2000; Nordenström et al., 2010). A lower birthrate has been described in women with CAH, and the following factors have been considered to contribute to this lower birthrate: the influence of low gonadotropins or high progesterone levels through inadequate glucocorticoid therapy, lack of interest in motherhood, and absence of sexuality (Frisén et al., 2009; Hagenfeldt et al., 2008; Jaaskelainen, Hippelainen, Kiekara, & Voutilainen, 2000; Stikkelbroeck et al., 2003). Until recently, there were no outcome studies of psychosexual development of adult males with CAH, as the high prenatal androgen levels in males are not thought to seriously influence gender development. A recent study by Nermoen, Husebye, Svartberg, and Løvås (2010) from Norway reported significantly impaired health-related quality of life and high rates of disability in both men and women with CAH. However, decreased fertility and living alone were more common in women.

Until the 1980s, most XY DSD individuals with severe under-androgenization (of androgen synthesis, PAIS, and mixed gonadal dysgenesis) were assigned to the female sex in line with the "optimal gender policy" (Money et al., 1955, 1994). Rates for gender dysphoria were reported in 25 % of XY individuals independent of the sex of rearing (Migeon et al., 2002). Whether improved medical care (including improved surgical procedures, sophisticated hormonal treatment, and psychosocial support) will have an impact on gender dysphoria and psychological well-being requires long-term follow-up and repeated cross-sectional representative studies large enough to demonstrate significant change.

6.3 Results from the German Clinical Evaluation Study

We now present the results of our own research from the clinical evaluation study by the DSD/intersexuality network (Lux, Kropf, Kleinemeier, Jürgensen, & Thyen, 2009) into the psychosexual development of people with DSD of various age ranges. Our purpose is to draw conclusions for the care and provision for people with DSD and their families. This was the first such study in Europe to include all forms of DSD (with the exception only of gonosomal disorders such as Turner or Klinefelter syndrome) as well as all age groups. Overall, more than 400 participants were recruited in Germany, Austria, and Switzerland to participate in the cross-sectional survey. All participants were interviewed in person and permission to review medical charts was required for participation in the study. No medical examination or laboratory testing took place at the time of the interview. This nationally supported study under the program of the German Research Ministry resulted in a Europe-wide cooperation. This succeeded through the formation of a broad European supervisory committee, which included among others Peggy Cohen-Kettenis, Claire Nihoul-Fekété, Justine Schober, Martin Ritzèn, Silvano Bertelloni, Ieuan Hughes, and Heino Meyer-Bahlburg. This successful cooperation was continued in two European studies—Euro DSD and DSD-Life. Euro DSD was founded in 2008–2011 as a collaborative project on the genetic causes, functional molecular biology, and pathophysiology of DSD. At its heart was the building of a European registry for DSD. DSD-Life is a clinical study started in 2013 which aims to investigate and compare long-term outcome in adequate numbers of adolescents and adults with different known genetic entities of DSD so as to develop evidence-based guidelines for the treatment of DSD. The influences and interrelations of sex assignment, genital surgery, hormone therapy, metabolism, fertility, psychological intervention, as well as cultural influences and patients' and parents' views on psychosocial adaption, health-related quality of life, and psychological well-being will be investigated. The intended long-term impact of the study is improvement of care and subsequently higher quality of life with better integration and participation of individuals with DSD in society.[1]

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[1] Euro DSD website: http://www.eurodsd.eu, last access 2013-01-12; information on DSD Life: http://cordis.europa.eu/search/index.cfm?fuseaction=proj.document&PJ_RCN=13271097

Following the Chicago Consensus (Hughes et al., 2006), we sought to capture both the extent of androgen exposure and the chosen sex of rearing. Because the investigated sample comprised a multiplicity of different diagnoses within the DSD spectrum, four subgroups were formed for the purposes of analysis:

1. Children with XY karyotype and androgen effects, who were reared as male.
2. Children with XY karyotype and androgen effects, who were reared as female.
3. Children with XY karyotype without androgen effects, who were reared as female.
4. Children with XX karyotype and androgen effects, who were reared as female.

6.3.1 Children Age 4 to 12 Years

From 2005 to 2007, 166 children age 4–12 years were studied with regard to their psychosexual development within the framework of the German clinical evaluation study. Of the study children, 55 (33 %) grew up as males: All of them had an XY karyotype and varying degrees of virilization deficit because of the disparate forms of their DSD (for a description of the study sample, see Jürgensen et al., 2010). Another 111 (66 %) children grew up as females: 36 of them had an XY karyotype and partial androgen effects (e.g., ovotesticular DSD, PAIS), 13 had an XY karyotype without androgen effects (e.g., CAIS), and 62 had an XX karyotype and androgen effects (all but one with CAH).

The study sample included 17 children whose sex of rearing had been changed. In all cases, this occurred not because of divergent gender role behavior or an existing gender dysphoria but because parents and doctors, sometimes after a rather late diagnosis, regarded the originally assigned gender as inappropriate in the long term. This parent- or physician-initiated change of sex of rearing occurred within the first year of life in 14 of the 17 children. In the case of the other three children, the sex of rearing change was carried out in the second or third year. The study included questions about gender identity (Gender Identity Interview for Children, Zucker et al., 1993), gender-typical preferences and attitude (Gender Role Questionnaire, IJntema, 1996; Child Behavior and Attitudes Questionnaire, Meyer-Bahlburg, Sandberg, Yager, Dolezal, & Ehrhardt, 1994), toy preference (toy to keep, modified from Berenbaum & Snyder, 1995), and peer preference (Jürgensen et al., 2010).

The results of the study show a high level of agreement between the gender identity of the study children and their sex of rearing, independent of the existence of androgen effects, karyotype, or evidence of virilization of the external genitalia. It is clear though that girls with XX DSD who have undergone a change of their sex of rearing from male to female are less certain of their gender identity than all other children in the study group. The fact that these children had initially been assigned a male sex of rearing indicates a very marked prenatal virilization.

The results for the gender role behavior of the children support the hypothesis that androgenic effects play a significant role in the development of typical male gender role behavior (Auyeung et al., 2009; Berenbaum & Bailey, 2003; Hall et al., 2004; Hines, 2006; Jürgensen et al., 2010). Clear differences in gender role behavior are shown between the DSD subgroups, depending upon whether there is evidence of androgen effects or not: Girls with evident androgen effects (both XX DSD and XY DSD) show significantly higher values for cross-gender behavior compared to girls without any androgen effects (XY DSD, i.e., CAIS) and boys (XY DSD) and girls from a (healthy) control group. Girls without androgen effects show typical female behavior. Boys did not have higher levels of cross-gender behavior than a (healthy) control group, in spite of their having lower androgen effects than boys without DSD. The extent to which this result supports the conclusion that the magnitude of the androgen effects has little influence on the degree of male-typical behavior remains an open question. Perhaps, an additional influence is that cross-gender behavior is perceived more negatively in boys than in girls, so that boys, feeling a stronger pressure to conform, suppress their cross-gender tendencies.

The study results in relation to peer preference show that, overall, children with DSD are less likely to have children of their own gender as a “best friend” or a playmate than children in the control group (Jürgensen et al., 2007, 2010). A pleasant result is that children with DSD just as frequently state that they have a best friend as children in the control group. There is no support for the suggestion that children with DSD feel ostracized because of their unusual physiology or, in some cases, their gender-atypical behavior.

Findings from childhood need to be interpreted with prudence: It must not be forgotten in the judgement of gender identity in children that this is only a snapshot and that the extent of the current adaptation is a reflection of the particular developmental challenge. Predictions for future development cannot be deduced from that, especially not in the case of adolescents with androgen biosynthesis disorders. In addition, individuals who struggled in childhood with their sex of rearing may develop gender dysphoria in adolescence or adulthood and possibly desire a sex change. The frequency of desiring a sex change depends upon the form of DSD, but it is in general higher than the societal average (Cohen-Kettenis, 2005; Kleinemeier et al., 2010; Slijper et al., 1998; Warne, 2008).

6.3.2 Adolescents

Because instruments that measure health-related outcomes in adolescents are limited, we developed our own questionnaires for the clinical evaluation study of the BMBF network. We aimed to measure physical and psychological well-being, gender identity, sexual experiences, and body image; Lindgren and Pauly (1975), for gender identity we used the Utrecht Gender Dysphoria Scale (Cohen-Kettenis & Van Goozen, 1997; Doorn, Kuiper, Verschoor, & Cohen-Kettenis, 1996; Steensma, Kreukels, Jürgensen, Thyen, et al., 2013). Sixty young people between the ages of 13 and 16 years participated in the study, among them 29 girls with XX DSD and partial androgen effects, 7 girls with XY DSD without androgen effects, 18 girls with XY DSD with androgen effects, and 6 boys with XY DSD and virilization deficit (cf., Lux et al., 2009). The results for gender identity in adolescents with DSD revealed no increased risk of gender dysphoria (Jürgensen et al., 2012). None of the adolescents had initiated a gender reassignment. In contradiction to the literature, we found no evidence of gender dysphoria or an excess of gender change in girls with XY DSD and increased androgen exposure. Nevertheless, these girls had the highest score for cross-gender behavior among all adolescents, although not at a clinically significant level. Closer examination revealed only a small number of girls with XY DSD (i.e., 17beta-HSD, 5alpha-RD) in the sample with a disruption of androgen biosynthesis, which can lead to unexpected virilization in puberty. In one female adolescent with XY DSD and androgen effects (with mixed gonadal dysgenesis), a change from male to female gender occurred as late as age 3. This young person had a raised score in the cross-gender scale. She showed a reduction in psychosocial well-being, which can be seen as evidence of poor adjustment and also of a possibly related gender dysphoria. Otherwise, the results of this study of young people with DSD confirm the hypothesis that the assigned gender in early childhood can be regarded as a reliable predictor of later gender identity.

Boys with DSD reported no concerns regarding their own sexuality, although they were less open about managing their DSD and frequently reported bad experiences with sexual contacts when they had occurred. Boys with DSD reported a negative body image in relation to their primary sex organs. This result clarifies the focus on the visible malformation of the penis. Differently from girls with XY DSD, boys with XY DSD experienced no discrepancy between the karyotype, internal genitalia, and the sex of rearing. We suggest that boys with DSD and their parents commonly regard “only” the malformation of the penis as an isolated problem, not considering possible phenomena such as gynecomastia, impotence, and infertility. However, the group of boys with DSD in our study was very small, which could explain the marginal results in the area of sexuality in boys.

The body image of girls with DSD did not differ from that of girls in the control group (Kleinemeier et al., 2010), in disagreement with the results of other studies (Krege et al., 2000; Warne et al., 2005; Wisniewski et al., 2001). This result corresponds to the better bodily well-being of girls with DSD compared to their peers in the clinical evaluation study (Kleinemeier et al., 2010). As is the case in the general population, the body image of adolescent girls with DSD is worse than that of adolescent boys with DSD (Davison & McCabe, 2006). We were surprised to find a relatively negative body image in girls with XY DSD without androgen effects (i.e., CAIS), as these girls have almost no visible signs of DSD and some even experience spontaneous breast development. But, Minto et al. (2003) had already shown that women with CAIS were discontented with their primary sex organs, even without observable gender-atypical signs. With these girls too, it appears that the discrepancy between gender role and karyotype leads to insecurity based upon their own body perception.

Interpreting the results of lacking experiences and dissatisfaction with sexuality in girls with DSD, we hypothesize insecurity regarding their own anatomy and the fear of having to tell potential partners about their DSD (cf., Kleinemeier et al., 2010). Girls are frequently ashamed of being different and want to be the same as their peers. The avoidance of sexual contact appears to be less problematic in adolescence than revealing the DSD to potential partners. The results for girls reflect the experiences of adults with DSD, whose sexual satisfaction is impaired, and support other studies which report reduced sexual activity among adolescents with DSD.

Identity development in puberty, especially the formation of sexual identity, is a decisive developmental process, which is likely to be more difficult in girls with DSD because of the discrepancy between karyotype and sex of rearing, prenatal androgen effects, and/or ambiguous genitalia. Moreover, because of the nonoccurrence of menstruation, girls with DSD are confronted earlier with the subject of being not fully developed, leading to hurtful feelings of inferiority and being different, whereas boys are often confronted later in adulthood (e.g., infertility). Possibly, they are conscious of a pressure to keep secret certain aspects of their DSD (e.g., lack of periods, infertility, and appearance of their genitalia) which again promotes the avoidance of sexual activity. Additionally, girls with CAH have to cope with regular medication, possible overweight, and growth problems.

6.3.3 Psychosexual Development of Adults with DSD

Adults ($n = 110$, age >16 year) participated in the German clinical evaluation study (Jürgensen et al., 2012). The results for the adult participants from the German clinical evaluation study are reported separately for 44 adult women with CAH (Köhler et al., unpublished) and 57 individuals with 46,XY DSD (Köhler et al., 2012). Data from a sample of female students and their relatives (age 18–57 year) from Hamburg served as controls (Schönbucher et al., 2012).

6.3.3.1 Psychosexual Development of Women with XX DSD (CAH)

No gender dysphoria was present in 43 women with CAH; however, one female with CAH changed to the male gender. A high proportion of women with CAH did not live in a partnership (70 %) or did not have sexual contact (32.5 %). Six women had their own children, and three had adopted children at a median age of 25 years (range 18–45). Only half of the women reported exclusively male sexual partners. Clitoris reduction had been performed in 82.5 % at a median age of 2.6 years. After genital surgery, cosmesis was evaluated as good by 71.4 % and sexual function by 65.7 % of operated individuals. Moreover, most women reported satisfaction with overall genital arousal (76.7 %) and clitoral arousal (75.9 %) following clitoris reduction. Fears of sexual contact were frequent (reported by 41.7 %). Sexual function was analyzed in a small group of 27 individuals who had sexual contact. Satisfaction with overall sex life was considerable in this group (83.3 %), but fear of sexual contact (33.3 %) and fear of injury during sexual intercourse (33.3 %) were high. Dyspareunia (29.6 %), problems with desire (18.5 %), arousal (14.8 %), and orgasm (37 %) were similar or lower than in controls (unpublished data). Thus, although the study sample was small, the results were rather positive in this group of women with CAH. However, the fear of sexual contact and intercourse was considerable. As sexual desire and arousal were not impaired in the study group, we hypothesize that prenatal androgen priming or later androgen imbalances have a positive effect on these feelings. However, larger representative groups of women with CAH who have had genital surgery with current techniques should be analyzed to support these hypotheses. Furthermore, the results should be evaluated according to genotype, as previous studies showed more impairment of sexual function in severely affected individuals with salt-wasting forms. In this type of CAH, the degree of hormonal disbalance and the degree of virilization are higher compared to the simple virilized types (Gastaud et al., 2007; Nordenström et al., 2010).

6.3.3.2 Psychosexual Development of Individuals with XY DSD

The German clinical evaluation study of DSD did not show increased gender dysphoria in 60 adults with different causes of XY DSD. One individual with PAIS changed gender in adulthood from male to female (Jürgensen et al., 2012). Three XY DSD individuals had changed from female sex of rearing to live as males but had not provided information about sexual experiences and had to be excluded from the analysis related to sexual experiences and genital surgery.

Ten individuals lived in the male gender and 47 lived in the female gender at the time of the interview. Although being registered in one of the two sexes, a total of 7 (all females) stated that they considered their own gender as a "third or other gender." About one third of female participants attended a support group (XY-women), whereas none of the men were members of a support group. Based on the absence or presence of partial androgen effects or genital constructive surgery, the female participants were divided into two subgroups: XY,DSD-P-F [individuals with partial androgen insensitivity (PAIS) and partial defects of androgen synthesis or gonadal dysgenesis] and XY,DSD-C-F (participants with complete androgen insensitivity (CAIS), complete gonadal dysgenesis, and complete defects of androgen synthesis).

Many individuals reported impairment of quality of sexual life; 37.5 % reported to be (very) dissatisfied with overall sex life and 44.2 % reported high levels of sexual anxieties.

Dissatisfaction with the surgical outcome (47.1 %) and clitoral arousal (47.4 %) was high in XY,DSD-P-F individuals after feminization surgery. The same group was more likely to report having female or both-sex partners (9.1 % and 18.2 %, respectively) compared to the control group and high rates of dyspareunia (56.5 %) in heterosexual contacts. In particular, most of the 11 individuals with CAIS were significantly dissatisfied with overall sex life, 9 reported significant problems with desire, 7 significant problems getting aroused, and 7 reported dyspareunia. The results are surprising as none of the participants with CAIS in this study had undergone constructive genital surgery. It can be hypothesized that lack of androgens after gonadectomy might be the cause of some sexual problems in individuals with CAIS as all had undergone gonadectomy and estrogen replacement therapy. Similar impairment of quality of sexual life has been reported in a previous German study in individuals with XY DSD (Schönbucher et al., 2012).

6.4 Conclusions and Implications for Clinical Care and Further Research

6.4.1 Issues Related to Pregnancy, Childbirth, and the Neonatal Period

The birth of a child with DSD or the diagnosis of a deviation from normal bodily gender development in childhood presents major challenges for parents and health professionals (Mieszczak, Houk, & Lee, 2009). Because of the growing availability of prenatal diagnoses to exclude child malformation or growth retardation, there is increased evidence that, even before birth, there may be a discrepancy between the child's chromosomal gender and phenotype (Russo et al., 2012). In other cases, a child is unexpectedly born with conspicuously ambiguous genitalia. The information process between the parents and the doctors places a particular requirement on the doctors, who are often not specialists, and other staff involved. In many cases, a joint decision must be made immediately after birth about the gender the child should grow up in and the other measures that need to be taken to give the child the greatest possible quality of life. For most parents (and doctors), this essentially means deciding which of the two genders, male or female, is to be assigned to the child, even in spite of the fact that there is a growing discussion in the literature about the possibility of an in-between sex and the recognition of an in-between sex by affected adults (see Chap. 4).

The possible course of future physical, emotional, and sexual development of individuals with DSD must also be kept in mind, in order to make the right decisions in childhood to achieve good lifelong outcomes for health, emotional, and social development (Sandberg, Gardner, & Cohen-Kettenis, 2012). Questions on the prognosis for psychosexual development therefore play an important role, particularly in the decision regarding the sex of rearing. These questions include gender identity, gender role behavior and (not forgetting that this is still a serious factor in some cultures) sexual orientation, reproductive capacity, and physical health, including the risk of malignancies Ahmed et al. (2011). The relative rarity of DSD in general and great variation of individual manifestations of the disorders mean that the evidence upon which decisions are based is very sparse. In general, there are few studies into the long-term psychosexual outcomes of the various treatment regimes; the few existing studies are distinguished by low subject numbers and/or methodological problems. This leads to parents, and generally also professionals, being uncertain whether their decisions for the sex of rearing were correct in the long term. This uncertainty can thereby result in a lack of self-confidence or lead to uncertainty in the child, e.g., if the parents frequently comment on the child's gender role behavior or seek to influence it. Repeated questions from the parents, whether the child really feels like a girl and not a boy (or vice versa), can make children insecure. It has not yet been investigated whether, and to what extent, this type of interaction induces possible deviations in childhood gender-typical behavior in children with DSD or insecurity in the child's own gender membership.

6.4.2 Childhood

Having a child with DSD presents a family with many essential decisions and questions. It is in no way a temporary "problem" arising after the birth of a child with ambiguous genitalia or following the diagnosis of a DSD, which is then resolved and ceases to exist. The special situation of the child remains lifelong and, as time passes, results in new challenges, uncertainties, and questions (Sanders, Carter, & Goodacre, 2012). The family should be offered continuous support along this path, either with medical questions, questions about explaining his/her own special situation to the child, questions of coping with particular social situations (e.g., with the unusual genital phenotype: diaper changing by other people, coping with nakedness in front of strangers, sports lessons, and class trips for older children), or by uncertainty about the psychosexual development of the child (Crissman et al., 2011). There is a need for a trained multi-professional team but, owing to the relative rarity of DSD, this service cannot be offered everywhere. Doctors and other professionals who have little experience with this subject should consult available expert groups and DSD teams.

Information from evidence-based research is indispensable to improve the quality of treatment and enables sound decisions about various treatment regimes. Studies of long-term outcomes are urgently required to ensure this. The relative rareness of DSD, and particularly of the various diagnoses within this spectrum, makes international cooperation by experts essential to carry out studies with a sufficiently broad evidence base. Care should ideally be carried out multidisciplinarily by doctors of various specialties, psychologists, and people with social pedagogical training (Hughes et al., 2006; Kogan et al., 2012; Moran & Karkazis, 2012).

6.4.3 Adolescence

The developmental period of adolescence is a sensitive one, an unstable phase of life which is marked by successfully coping with developmental tasks as well as stress and discontinuity (Schulenberg, Maggs, & Hurrelman, 1997). The intensification of gender determination results in a multiplicity of challenges for adolescents with DSD. Adolescents' central developmental tasks are, among others, the acceptance of physical changes related to puberty, taking on male/female gender roles, building sexual relationships, developing a comprehension of partnership and family, and the building of a consistent identity. It is clear that symptoms of DSD interfere with the developmental tasks of adolescents (Liao, Tacconelli, Wood, Conway, & Creighton, 2010).

Adolescents, in particular, require support with questions of shame and stigmatization, as well as coping with the normative pressure with which they live. The treatment teams must be proactive about these points because adolescents only rarely speak about them. The majority of adolescents do not report information about their sexual problems, possible problems with their appearance, and the side effects of the medical treatment. Treatment teams must work through these themes with the adolescents cautiously and with empathy. It is the job of the specialists to take the anxieties, problems, and requirements of adolescents seriously. The treatment of adolescents with DSD is grounded in child and adolescent medicine where there remain difficulties associated with the special transitional state of adolescents. It is commonly difficult for specialists to understand the developmental step from childhood to adolescence, to change their own approach, and to transfer more responsibility from the parents to the adolescent. The aim should be to regard the adolescents as the experts and support them in this development. A firm part of this is, above all, an honest and age-appropriate explanation of each adolescent's own physical development.

6.4.4 Ethical Issues Related to Early Surgery

Prenatal deficit of androgens or decreased androgen action in XY DSD and prenatal excess of androgens in XX DSD do not only have effects on sexual priming of the brain (Swaab et al., 2007) but also result in atypical development of the genitalia. Several aspects need to be considered in the individual but also in the professional discourse about necessary (i.e., preventing serious health problems), corrective (i.e., increasing functionality), or cosmetic (i.e., improving appearance) surgical interventions.

Constructive genital surgery may be necessary to allow for heterosexual intercourse in many cases; however, that may not be an anticipated wish in all patients and the results of surgery are often poor. Objectively good surgical results were reported in a recent Dutch study in a mix of individuals with XY DSD and CAH (Callens et al., 2012). However, 60 % needed re-surgery in puberty following a single-stage procedure in early childhood. Many patients showed impairment on the female sexual function index and were at risk of developing sexual dysfunction (66 %). At a median age of 26, many patients had not ever had sexual intercourse (41 %). Interestingly, nonoperated patients with CAIS and complete gonadal dysgenesis were significantly more dissatisfied with sexual life than operated women with XY DSD or CAH, a result similar to the two German studies. Moreover, a large proportion of women mentioned problems of coping with the diagnosis, distress of infertility, and suffering from societal ignorance and taboo. It can be assumed that these are the major contributory factors in the impairment of sexual life in XY DSD (Callens et al., 2012).

Clinical studies on outcomes with current surgical methods are necessary to improve outcomes and to allow for recommendations. Currently, feminizing genital surgery is not indicated in very young children with XY DSD. Constructive genital surgery should be minimized and performed in adolescence or adulthood by a specialized surgeon with the patients' consent. The American consensus groups for management of CAH suggested early vaginoplasty between the second and sixth month, as results are predicted to be better due to the estrogen effects of pregnancy and mini-puberty. Clitoroplasty should be considered only in severely virilized individuals (Joint LWPES/ESPE CAH Working Group, 2002; Speiser et al., 2010). It should not be assumed that a larger clitoris impairs sexual life. Delaying vaginoplasty until puberty is a second option. Puberty is a period that is also optimal due to estrogenization of the genitalia, and from an ethical point of view, the procedure can be performed with the patient's consent (Creighton et al., 2003). Evidence of better outcome of early vaginoplasty is thus far lacking. Children and adolescents should be informed in an age-appropriate manner about the effect of their prenatal androgens on their genitalia as well as issues arising from surgery. Psychological support should be given especially in puberty and around the time of surgery. Peer contacts with other DSD individuals should be encouraged, as discussing with peers can be as helpful as nonprofessional support. Sexual therapy might be needed in puberty and adulthood.

In general, recommendations for clinical care depend on the age of the child, the family, and the cultural and the societal context. Multidisciplinary care is mandatory from childhood to adulthood (Hughes et al., 2006).

6.4.5 Human Rights Perspective

In February 2012, the German Ethical Committee published an extensive statement dealing with the legal, social, and medical aspects of intersexuality/DSD (Deutscher Ethikrat 2012). Two years of intense work followed the commission of the UN committee, who issued the "Convention on the Elimination of All Forms of Discrimination Against Women" (CEDAW), and tasked the German government to ensure that individuals be protected from violations of human rights. The German Society for Pediatric Endocrinology and Diabetology (DGKED) explicitly supports the standpoint of the Ethical Committee and commissioned an article specifically to discuss the issues related to the care for children and their families (Birnbaum et al., 2012). The work of the German Ethical Committee and the publication will build the foundations for a more encompassing future consensus for the treatment of DSD and dealing with intersexuality.

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Part III
Gender Dysphoria

Chapter 7
Gender Identity Diagnoses: History and Controversies

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Abstract This chapter begins with a review of psychiatric and medical theorizing about transsexualism and transgender presentations since the nineteenth century. Until the middle of the twentieth century, with rare exceptions, transgender presentations were usually classified as "psychopathological." By the middle of the twentieth century, transsexualism and sex reassignment surgery became more common and more available, leading to greater popular, medical, and psychiatric awareness of the concepts of *gender identity* and recognition of an increasing number of people wishing to "cross over" from their birth-assigned sex to another. In the twenty-first century, international expert guidelines support transition in carefully evaluated individuals, although the healthcare systems in only a minority of countries now cover needed medical services for sex reassignment.

This chapter then goes on to review the shifting placement of gender identity and gender role diagnoses over time within both the World Health Organisation's (WHO) *International Statistical Classification of Diseases* (ICD) and the American Psychiatric Association's (APA) *Diagnostic and Statistical Manual* (DSM). In recent years, gender identity diagnoses of both the ICD and DSM have generated several controversies, reflecting not only differing perspectives of mental health professions from those of transgender advocacy groups but also differences of opinion within the lesbian, gay, bisexual, and transgender community (LGBT) itself. These controversies are briefly reviewed. The professionals charged with ICD-11 and DSM-5 revisions have attempted to balance both concerns about retaining access to care and perpetuating the stigma associated with a mental disorder diagnosis. This chapter reviews how the diagnostic classification of disorders related to transgender identity has been an area long characterized by constant shifts in placement and renaming of these diagnoses in various editions of the ICD

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and DSM. Therefore, another name change and another category move would be more reflective of current thinking in this area of clinical work.

7.1 Introduction

Psychiatric and medical theorizing about transsexualism and transgender presentations began in the nineteenth century. Until the middle of the twentieth century, with rare exceptions, transgender presentations were usually classified as “psychopathological.” Krafft-Ebing (1886) took this view and his *Psychopathia Sexualis* might be thought of as an early psychiatric diagnostic manual that documented cases of individuals who desired to live as members of the other sex and those who had been born to one sex and were living as members of the other. In the chapter entitled “General Pathology” he presented, in Latin, an autobiographical case (#129) of what he called *Metamorphosis Sexualis Paranoia*:

> … at the age of twelve or thirteen, I had a definite feeling of preferring to be a young lady… But I was careful not to allow this to be noticed; and yet I am sure that I should not have shrunk from the castration-knife, could I have thus attained my desire … Girls liked my society; and though I should have preferred to have been with them constantly, I avoided them when I could, for I had to exaggerate in order not to spear feminine. In my heart I always envied them … I remember, when fifteen, to have first expressed to a friend the wish to be a girl. In answer to his question, I could not give the reason why … At the high school I finally once had coitus; I felt that I would rather have lain under the prostitute and would have preferred to exchange my member for her genitals … Thus I went through life, such as it was, never satisfied with myself, full of dissatisfaction with the world … (pp. 263–266).

Krafft-Ebing then goes on to describe another case (#130) of *Metamorphosis Sexualis Paranoia*, this time in a natal woman:

> As a girl Mrs. X had decided inclinations for boys’ sports. So long as she wore short dresses she used to rove about the fields and woods in the freest manner, and limbed the most dangerous rocks and cliffs. She had no taste for dresses and finery … Otherwise nothing betrayed her homosexual inclinations. Up to her marriage (at the age of twenty one) she could not recall to mind a single instance in which she felt herself drawn to persons of her own sex … At the age of thirty-six she had an apoplectic stroke which confined her to bed for two years … She refused to wear anymore a lady’s nightdress or a lady’s cap, and put away her bracelets, earrings and fans. Her maid and her dressmaker noticed a different odor coming from her person; her voice also grew deeper, rougher and quite masculine. When the patient was finally able to leave her bed, the female gait had altered, feminine gestures and movements in her female attire were forced, and she could no longer bear to wear a veil over her face. Her former period of life spent as a woman seemed strange to her, as if it did not belong to her existence at all; she could play no longer the role of woman (pp. 276–278).

It was typical of these early theories to conflate transgender presentations with homosexuality. For example, Ulrichs’ (1864) *third sex theory* of men’s spirits in women’s bodies (*urningen*) and women’s spirits in female bodies (*urnings*) was his explanation of the “cause” of homosexuality (several years before the latter term was actually coined). Yet a female spirit in a male body bears narrative kinship with twentieth-century theories of transsexualism. So does Freud's (1910) attribution of Leonardo da Vinci's homosexuality to his being "a man who loved like a woman," that is, someone who identified with his mother. From a narrative perspective, a man's identification with his mother is not altogether unlike a woman's spirit trapped in a man's body. Both theories explain homosexuality based on the binary belief that there are only two genders and that some quality of one gender has found its way into the other.

It is Magnus Hirschfeld (1923) who is credited with being first to distinguish the desires of homosexuality (to have partners of the same sex) from those of transsexualism (to live as the other sex). However, those distinctions were not broadly accepted until decades later. Further, although physicians in Europe had begun performing sex reassignment surgery (SRS) in the 1920s, transsexualism and SRS sensationally really entered the popular imagination when the US media reported on the case of George Jorgensen. Jorgensen went to Denmark as a natal man and returned to the USA in 1952 as a trans woman with a new body and a new name: Christine (Jorgensen, 1967). Shortly thereafter, the Danish physicians who participated in Jorgensen's SRS published a report of her medical and surgical treatment in the *Journal of the American Medical Association* (Hamburger, Stürup, & Dahl-Iversen, 1953).

The publicity surrounding Jorgensen's transition would eventually lead to greater popular, medical, and psychiatric awareness of the concepts of *gender identity*, and later terms like *expressed gender* and *experienced gender*, as well as recognition of an increasing number of people wishing to "cross over" from their birth-assigned sex to another. Within professional circles, changes in attitude toward transition were spearheaded by the pioneering work of Harry Benjamin (1966), John Money (1994), Robert Stoller (1964), and Richard Green (1974). Increased public discussions of sex reassignment and gender identity would provide those who would eventually come to identify as *transsexual* or transgender with a category and a name for their feelings and desires (Denny, 2002). In time, what was once considered an exceedingly rare condition gradually became more publicly visible, and in recent years, an increasing number of nations, provinces, and municipalities have enacted laws establishing "gender identity" as a protected group along the line of categories like race, ethnicity, age, sex, and sexual orientation.

However, these changes did not take place overnight. At the time of Jorgensen's 1950s SRS and for several decades afterward, many mental health practitioners were critical of sex reassignment as a treatment for gender dysphoric individuals (e.g., Hertoft & Sørensen, 1978; McHugh, 1992; Socarides, 1969). As much psychiatric theorizing of that time continued to conflate sexual orientation and gender identity, many physicians and psychiatrists criticized using surgery and hormones to irreversibly—and in their view incorrectly—treat people suffering from what they perceived to be either a severe neurotic or psychotic, delusional condition in need of psychotherapy and "reality testing." This was the mainstream view of the time and it was captured in a 1960s survey of 400 physicians that included psychiatrists, urologists, gynecologists, and general medical practitioners asked to give their professional opinions about what to do in the case of an individual seeking SRS. The case was as follows:

> Since early childhood, this 30-year-old biological male has been very effeminate in his mannerisms, interests, and daydreams. His sexual desires have always been directed toward other males. He would like to be able to dress exclusively in woman's clothes. This person feels inwardly and insists to the world that he is a female trapped in a male body. He is convinced that he can only be happy if he is operated on to make his body look like that of a woman. Specifically, he requests the removal of both testes, his penis, and the creation of an artificial vagina (all of which can, in fact, be done surgically). He also requests that his breasts be made to appear like a woman's, either surgically or by the use of hormones (this, too, is medically possible) (Green, 1969, p. 236).

Green summarized the survey's findings as follows:

> Eight percent [8%] of the respondents considered the transsexual "severely neurotic" and fifteen percent [15%] considered the person "psychotic." The majority of the responding physicians were opposed to the transsexual's request for sex reassignment even when the patient was judged nonpsychotic by a psychiatrist, had undergone two years of psychotherapy, had convinced the treating psychiatrist of the indications for surgery, and would probably commit suicide if denied sex reassignment. Physicians were opposed to the procedure because of legal, professional, and moral and/or religious reasons. In contrast to the conservatism with which granting of sex-reassignment procedures was viewed, there was a paradoxical liberalism in the approach to these patients should they already have been successful in obtaining their surgery elsewhere. Among the respondents, three quarters [75%] were willing to allow the postoperative patient to change legal papers such as a birth certificate and to marry in the new gender, and one-half [50%] would allow the person to adopt a child as a parent in the new gender (pp. 241–242).

Although these were once the prevailing views, they are no longer part of the mainstream of psychiatric or general medical thought and practice. In the twenty-first century, international expert guidelines support transition in carefully evaluated individuals (WPATH, 2011), although the healthcare systems in an only minority of countries around the world now cover needed medical services for sex reassignment (Kreukels et al., 2012; Yogyakarta Principles, 2007).

7.2 History of Diagnostic Placement: ICD and DSM

The placement of gender identity and gender role diagnoses has shifted over time within both the World Health Organisation's (WHO) *International Statistical Classification of Diseases* (ICD) and the American Psychiatric Association's (APA) *Diagnostic and Statistical Manual of Mental Disorders* (DSM).

Table 7.1 summarizes the placements of gender diagnoses in the ICD and in the DSM.

7.2.1 ICD

ICD-6, approved in 1948, was the first version of the ICD published by WHO, the first version of ICD to include a classification of morbidity, and the first version that included a classification of mental disorders. Prior to ICD-6 and the founding of

Table 7.1 Gender diagnoses in the ICD and DSM

Year	ICD	DSM	Parent category	Diagnosis name
1948	ICD-6	–	N/A	N/A
1952	–	DSM-I	N/A	N/A
1955	ICD-7	–	N/A	N/A
1965	ICD-8	–	Sexual deviations	Transvestitism
1968	–	DSM-II	Sexual deviations	Transsexualism
1975	ICD-9	–	Sexual deviations	Transvestism
				Trans-sexualism (sic)
1980	–	DSM-III	Psychosexual disorders	Transsexualism
				Gender identity disorder of childhood
1987	–	DSM-III-R	Disorders usually first evident in infancy, childhood, or adolescence	Transsexualism
				Gender identity disorder of childhood
				Gender identity disorder of adolescence and adulthood, nontranssexual type
1990	ICD-10	–	Gender identity disorders	Transsexualism
				Dual-role transvestism
				Gender identity disorder of childhood
				Other gender identity disorders
				Gender identity disorder, unspecified
1994	–	DSM-IV	Sexual and gender identity disorders	Gender identity disorder in adolescents or adults
				Gender identity disorder in children
2000	–	DSM-IV-TR	Sexual and gender identity disorders	Gender identity disorder in adolescents or adults
				Gender identity disorder in children
2013	–	DSM-5	Gender dysphoria	Gender dysphoria in adolescents or adults
				Gender dysphoria in children
2015	ICD-11	–	?	Gender incongruence of adolescents and adults
				Gender incongruence of children (proposed)

WHO, ICD was exclusively a mortality classification. Mental disorders in general and sexual disorders in particular were not considered to be causes of mortality, so they were not included in these classifications.

In ICD-6 (1948), there is no reference to the diagnosis of transsexualism; nor does it appear in ICD-7 (1955).[1] The ICD-8 (1965), reflecting changing clinical and theoretical views, separated out *sexual deviations* from *personality disorders*. The sexual deviations included the new diagnosis of *transvestitism* for the first time (Table 7.1). Definitions of diagnostic categories were not provided in ICD-8, so the intended meaning of *transvestitism* is not entirely clear. Historically, however, an alternative spelling of *transvestism* was used as an early synonym for what later came to be known as transsexualism (i.e., Hamburger et al. (1953) use the term transvestism in their description of Jorgensen's surgery) and that may have been part of the reason for placing it in ICD-8.

Further change occurred in the ICD-9 (1975), in which transvestitism was replaced by *transvestism*. It was defined as a "Sexual deviation in which sexual pleasure is derived from dressing in clothes of the opposite sex. There is no consistent attempt to take on the identity or behaviour of the opposite sex." While still in the sexual deviation category, it was now a separate and exclusionary diagnosis for a newly added diagnosis of *trans-sexualism* (sic) (Table 7.1). Again, it is reasonable to assume that this new separation was made to accommodate a growing body of research about clinical presentations and treatment of transsexualism in the previous two decades.

The ICD-10 (1990) saw a significant reorganization of the classification system and some new gender diagnoses that reflected a growing body of clinical experience and research. Under *disorders of adult behaviour and personality* appears a new category of *gender identity disorders* (F64) which includes five diagnoses: *transsexualism*, *dual-role transvestism*, *gender identity disorder of childhood*, *other gender identity disorders*, and *gender identity disorder*, *unspecified* (see Table 7.1).

At the time of this writing, there have been preliminary proposals made for the ICD-11 revision currently underway, and the ICD revision is scheduled to be published in 2015. WHO's Working Group on the Classification of Sexual Disorders and Sexual Health (WGSDSH) has been charged with evaluating clinical and research data to inform revision of diagnostic categories related to sexuality and gender identity currently in the Mental and Behavioural Disorders chapter of ICD-10, and with making recommendations regarding whether and how these categories should be represented in ICD-11. At present, the preliminary proposals include a name change of the diagnosis to *gender incongruence* and a recommendation that the entire diagnostic category be moved outside the mental disorders section of the ICD. Whether that would be in a new section of its own or elsewhere in the ICD remains to be determined (Drescher, Cohen-Kettenis, & Winter, 2012).

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[1] By way of contrast, and as previously noted, sexual orientation and gender identity were often conflated at that time; a diagnosis called *homosexuality* does appear in both ICD-6 and ICD-7. Homosexuality is listed as an example of the diagnostic category *sexual deviation*, which is further classified as a *pathologic personality* under the supra category of *disorders of character, behaviour, and intelligence*. The diagnosis of homosexuality persisted into ICD-8 and ICD-9 but was removed from ICD-10 and replaced by *egodystonic sexual orientation* (Drescher, 2010).

7.2.2 DSM

In a similar if not entirely parallel manner, gender identity diagnoses underwent category migration and renaming in the APA's Diagnostic and Statistical Manual (DSM). It is also a history that illustrates the shifting views about what to call the diagnosis, what it means, and where to place it over time. As in the ICDs 6–8, no mention of the diagnosis exists in either the DSM-I or DSM-II (1952, 1968). In 1980, however, a revamped DSM-III abandoned the psychodynamic theorizing of the first two manuals and adopted a neo-Kraepelian, descriptive, symptom-based framework drawing upon contemporary research findings. Zucker and Spitzer (2005) describe the environment leading to gender diagnoses being included in the DSM:

> During the 1960s, North American psychiatry had begun to take a look at the phenomenon of transsexualism in adults [see, for example, Green and Money (1969) and Stoller (1968)]. It became apparent that psychiatrists and other mental-health professionals had become increasingly aware of the phenomenon, that is, of adult patients reporting substantial distress about their gender identity and seeking treatment for it, typically hormonal and surgical sex-reassignment. Indeed, there were enough observed cases that it was possible in the 1960s to establish the first university- and hospital-based gender identity clinics for adults. Many clinicians and researchers were writing about transsexualism, and by 1980, there was a large enough database to support its uniqueness as a clinical entity and a great deal of empirical research that examined its phenomenology, natural history, psychologic and biologic correlates, and so forth. Thus, by the time DSM-III was in its planning phase in the mid-1970s, there were sufficient clinical data available to describe the phenomenon, to propose diagnostic criteria, and so on (p. 37).

Zucker and Spitzer (2005) also summarize the vicissitudes of the current gender diagnoses from DSM-III through DSM-IV-TR:

> In the third edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-III) [1980], there appeared for the first time two psychiatric diagnoses pertaining to gender dysphoria in children, adolescents, and adults: gender identity disorder of childhood (GIDC) and transsexualism (the latter was to be used for adolescents and adults). In the DSM-III-R [1987], a third diagnosis was added: gender identity disorder of adolescence and adulthood, nontranssexual type. In DSM-IV [1994, and DSM-IV-TR (2000)], this last diagnosis was eliminated ("sunsetted"), and the diagnoses of GIDC and transsexualism were collapsed into one overarching diagnosis, gender identity disorder (GID), with different criteria sets for children versus adolescents and adults (p. 32).

It should be further added that in addition to name changes, the diagnostic category migrated within DSM chapters. In DSM-III (1980), both GIDC and transsexualism are listed among the *psychosexual disorders*. In DSM-III-R (1987), both are moved to a category of *disorders usually first evident in infancy*, *childhood, or adolescence.* In DSM-IV (1994) and DSM-IV-TR (2000), they are moved again to a new parent category, *sexual and gender identity disorders*, and transsexualism is renamed *gender identity disorder in adolescents or adults*. It is then clustered with the paraphilias and sexual dysfunctions (Table 7.1).

At the time of this writing, the DSM-5 is in the closing stages of preparation for 2013 publication. The accepted proposals of the DSM-5 Workgroup on Sexual and

Gender Identity Disorders for the DSM-5 (APA, 2013) are (1) to have one overarching diagnosis, *gender dysphoria* (*GD*); (2) to have GD include separate, developmentally appropriate criteria sets for children (*gender dysphoria in children*) and another for adolescents and adults (*gender dysphoria in adolescents and adults*); and (3) to move GD into a separate category separated from sexual dysfunctions and paraphilias.[2]

7.3 Controversies

In recent years, gender identity diagnoses of both the ICD and DSM have generated several controversies. These controversies reflect not only the differing perspectives of mental health professions from those of transgender advocacy groups but also differences of opinion within the lesbian, gay, bisexual, and transgender community (LGBT) itself.

For example, some LGBT advocacy groups have argued that it is wrong for psychiatrists and other mental health professionals to label variations of gender expression as symptoms of a mental disorder. These advocates have argued for removal of the diagnoses from the diagnostic manuals.

Others decry as unscientific, unethical, and misguided the use of the childhood gender identity diagnoses to justify clinical efforts aimed at getting them to reject their expressed gender identity and to accept the sex (and gender) they were assigned at birth. In doing so, they have compared clinical efforts to treat gender-variant children with clinical efforts to change homosexuality [Pickstone-Taylor, 2003; see Drescher (2010) for discussion of this issue]. The controversies surrounding the treatment of children and young adolescents, however, raise many complex issues which are not entirely the same as those involving the treatment of older adolescents and adults, and consequently, a detailed discussion of those issues is beyond the scope of this chapter [see Drescher and Byne (2013) for an interdisciplinary discussion of clinical ethical issues in the treatment of children and adolescents].

Alternatively, other advocacy groups have raised concerns that removing the adolescent and adult gender identity diagnoses would lead to loss of private and public insurance coverage for necessary medical and surgical treatment, since all medical treatments require some form of diagnostic coding. In addition, at least in the United States, removing the gender identity diagnoses entirely from the diagnostic manual would lead to the loss of a potent and increasingly successful argument of medical necessity in legal cases challenging denial of medical treatment to transgender individuals. Consequently, in both the DSM-5 and ICD-11 revision processes, the professionals involved have tried to find a balance between the competing issues of stigma versus access to care (Drescher, 2010).

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[2] The proposed DSM-5 revisions of this category are available on line at http://www.dsm5.org/ProposedRevision/Pages/GenderDysphoria.aspx. Also see Cohen-Kettenis and Pfäfflin (2010), Drescher (2010), Meyer-Bahlburg (2010), and Zucker (2010).

7.4 Stigma

The relationship between psychiatric diagnosis and stigma is documented lucidly by the history of the removal of homosexuality from the DSM-II in 1973 (Bayer, 1987). In the aftermath of the APA decision, psychiatry abandoned its historical participation in stigmatizing homosexuality. Those who accepted scientific authority on such matters gradually came to accept the APA's position, and a new cultural perspective emerged: (1) if homosexuality is not an illness, and (2) if one does not literally accept biblical prohibitions against homosexuality, and (3) if contemporary, secular democracy separates church and state, and (4) if openly gay people are able and prepared to function as productive citizens, then what is wrong with being gay? And if there is nothing wrong with being gay, then what moral and legal principles should the larger society endorse in helping gay people openly live their lives? This led to a historically unprecedented social acceptance of gay men and women across much of the world which, in many countries and cultures, has culminated in the contemporary social and policy debates about gay civil rights and marriage equality (Drescher, 2012).

The movement for transgender civil rights began more slowly but followed, nevertheless, in the wake of the larger gay rights movement (Drescher, 2010). By the late 1990s, trans-inclusion had increasingly become a focus of LGBT rights groups, and support by these groups for transgender rights continues to this day. Given that the removal of homosexuality from the DSM was a watershed in the gay civil rights movement, a similar goal is being sought for transgender people as well. For example, as the ICD revision process has unfolded, many advocates, several countries, the Council of Europe Commissioner for Human Rights (2009), and the European Parliament (2011) have taken strong positions that issues related to transgender identity should not be classified as mental disorders in the ICD-11. The European Parliament resolution *"roundly condemns the fact that homosexuality, bisexuality and transsexuality are still regarded as mental illnesses by some countries, including within the EU, and calls on states to combat this; calls in particular for the depsychiatrisation of the transsexual, transgender, journey, for free choice of care providers, for changing identity to be simplified, and for costs to be met by social security schemes."* The document goes on and *"calls on the Commission and the World Health Organisation to withdraw gender identity disorders from the list of mental and behavioural disorders, and to ensure a non-pathologising reclassification in the negotiations on the 11th version of the International Classification of Diseases* (*ICD-11*)*."*

Similar concerns about diagnostic retention were raised in the DSM revision process. For example, the World Professional Association for Transgender Health (WPATH) called for depathologization and removal of transgender diagnoses from the DSM-5 (Knudson, DeCuypere, & Bockting, 2010). In a survey by the DSM-5 GID subworkgroup of 201 organizations concerned with the welfare of transgender people from North America, Europe, Africa, Asia, Oceania, and Latin America, a majority (55.8 %) believed the diagnosis should be removed from the DSM (which is, of course, a classification consisting exclusively of mental disorders). The major reason for wanting to keep the diagnosis in the DSM was healthcare reimbursement. Regardless of whether groups were for or against the removal of the diagnosis from the mental disorders classification, the survey revealed a broad consensus that if the diagnosis remains in the DSM, there needs to be an overhaul of the name, criteria, and language to minimize stigmatization of transgender individuals (Vance et al., 2010).

While reducing the stigmatization of mental disorders is important, arguing to remove a diagnostic category from the DSM or the mental disorders section of the ICD simply because mental disorders are stigmatized is neither compelling nor persuasive. Stigmatization of individuals with psychiatric disorders is a social problem across cultures. Organized psychiatry and other mental health professionals have spent decades trying to reduce the stigma of psychiatric illness in order to increase access to care and to encourage people to avail themselves of mental health services. Mental health professions are themselves stigmatized because of their association with the conditions affecting the populations they treat. Further, there is a general consensus that mental disorders are health conditions; otherwise, why would they be in the ICD? One unintended consequence of belaboring distinctions between medicine and psychiatry, and this is a wider problem also beyond the scope of this chapter, is the perpetuation of existing stigma and prejudices against the mentally ill (Drescher, 2010).

However, the combined stigmatization of being transgender and of having a mental disorder diagnosis creates a doubly burdensome situation for this population, and it would be fair to say that this situation supports arguments for moving the category out of the mental disorders section.

7.5 Issues of Placement

From a historical perspective, the classification of gender diagnoses as mental disorders was serendipitous. If, in the mid-twentieth century, the narrative had been that transsexualism was related to a “hormone imbalance” rather than being a “sexual deviation,” the category could very well have been placed in the ICD-10 chapter on “Endocrine, nutritional, and metabolic diseases.” In fact, the etiology of the condition was unknown when placement decisions were made in the past and remains unknown now. Further, there are no scientifically based criteria to differentiate normal and pathological gender identity, and the manner in which *any* gender identity develops remains unknown and a matter of theoretical speculation. The extant scientific database cannot empirically answer the question of whether this diagnosis is purely a “mental disorder” or a disorder with another physical cause. There are a growing number of studies that posit physical rather than mental causes of transgender presentations (Berglund, Lindström, Dhejne-Helmy, & Savic, 2008; Garcia-Falgueras & Swaab, 2008; Herbert, 2008; Kruijver et al., 2000; Rametti et al., 2011; Schöning et al., 2010; Zhou, Hofman, Gooren, & Swaab, 1995).

7.5.1 Medical Diagnosis

It is possible to classify gender identity diagnoses as purely medical conditions. In 2010, for example, France removed transsexualism from its mental disorders section and placed it in a category known as *maladie rare* (Brunet, 2010). Another alternative would be placing these diagnoses in either the endocrinological or genitourinary sections. The latter approach solves the problem of the diagnoses being stigmatized as a mental disorder while still allowing access to care. On the other hand, much of the healthcare accessed by this patient population is not directly related to endocrinology, although the case could be made that other health and mental health services required are indirectly related in many cases. A genitourinary placement is also problematic since many people who might be diagnosed do not seek or require such surgery.

7.5.2 V- and Z-Codes

DSM's V-codes and ICD's Z-codes are used to indicate conditions or clinical situations that might come to the attention of a mental health professional but are not in and of themselves considered to be mental disorders. Such a change in the diagnostic systems would serve the purpose of depathologizing and destigmatizing the category; it would be neither a mental disorder nor a physical one (physical disorders are also stigmatized, although not typically as much as mental ones). While this would reduce stigma, such a move is likely to interfere with access to care as third-party payers rarely reimburse V- and Z-codes.

7.6 Conclusion

Since 2008, this author has been a member of the DSM-5 Workgroup on Sexual and Gender Identity Disorders and, since 2011, a member of the ICD-11 Working Group on the Classification of Sexual Disorders and Sexual Health. In the midst of the DSM-5 deliberations, this author made the argument for retention of the mental disorder diagnosis:

> How should APA proceed? Physicians need to take to heart the dictum "first do no harm." This guides many clinical encounters in which physicians and patients must make treatment choices, all of which are potentially fraught with harm. In those cases, the best approach is to make choices that maximize benefits and minimize harm (or side effects). At this moment in time, I believe the less harmful choice would be retaining and modifying the adolescent and adult GID diagnostic criteria to make them more narrowly inclusive of individuals who are distressed about the dissonance between their anatomical and psychological gender (Drescher, 2010, p. 454).

The principles of reducing stigma and reducing false-positive diagnoses, such as labeling non-distressed expressions of gender variance as mental disorders, did in fact guide the workgroup in its deliberations. However, as a member of the ICD Working Group on Sexual Disorders and Sexual Health, the opportunity arose to further reduce stigma by moving the gender identity diagnoses out of the mental disorders section entirely (Drescher et al., 2012). Such a move would not be entirely unprecedented. As this chapter has shown, the diagnostic classification of disorders related to transgender identity has been an area long characterized by constant shifts in placement and renaming of these diagnoses in various editions of the ICD and DSM. Another name change and another category move would simply be more reflective of current thinking in this area. There is also a strong possibility that such a change would lead to the removal of the gender dysphoria diagnoses from the DSM, reflecting the changing values in many cultures where gender variance is increasingly accepted as a normal part of life.

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Chapter 8
Care for Gender-Dysphoric Children

Domenico Di Ceglie

> *When you are studying any matter… ask yourself what are the facts… Never let yourself be diverted by what you wish to believe.*
>
> *(Bertrand Russell)*

Abstract This chapter describes the approach to the care of children with gender dysphoria as developed in the Gender Identity Development Service (GIDS) in London. It makes references to the current and historical context of the early services in Toronto and Utrecht/Amsterdam. The reasons for offering professional help are discussed in a context that challenges stereotyping and stigmatization. The historical background of the service is described in relation to Toronto and Utrecht/Amsterdam.

The GIDS is a countrywide specialist resource and has developed a network model of care that involves partnership with local services to ensure a holistic approach, particularly in cases which have associated psychological difficulties. The specialist GIDS assessment and therapeutic work is outlined. Gender variant role expression in childhood, which is a current topical issue, is discussed. The author highlights the professional role of engaging families in reflective practice. Finally, the chapter concludes that, as new clinical and research evidence emerge, new models of care will be developed. These models will have to ensure greater equality of care for the diverse needs of children with gender dysphoria/variance and engage more with culturally diverse communities.

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8.1 Introduction

In this chapter, I describe the approach to the care of children with gender dysphoria as developed in the Gender Identity Development Service (GIDS) in London. However, some aspects represent a personal view. In describing its development, I also make references to the current and historical context of the early services in Toronto and Utrecht/Amsterdam.

I begin with a metaphor to introduce a reflection on the nature of gender diversity in children. Recently, the Chinese artist Ai Weiwei created an installation at the Tate Modern in London which he called sunflower seeds. This extensive mass of seeds seen at a distance looks uniform and undifferentiated, but as one looks a bit more closely, the individuality of each seed becomes more and more evident. There are no two seeds which are the same (see Figs. 8.1 and 8.2).

Ai Weiwei explained that each porcelain seed was individually painted by workers, who collaborated in the project, and not by a machine. Each seed required between three and six strokes according to the ability or the style of each collaborator. Therefore, the diversity of the seeds was the result of the creative process. In a way similar to this work of art, children who present with atypical gender identity development, DSM-IV-TR defined "gender identity disorder" (GID) (American Psychiatric Association, 1994), all present differently within this category and not as part of a stereotype. It is therefore important to offer different types of help

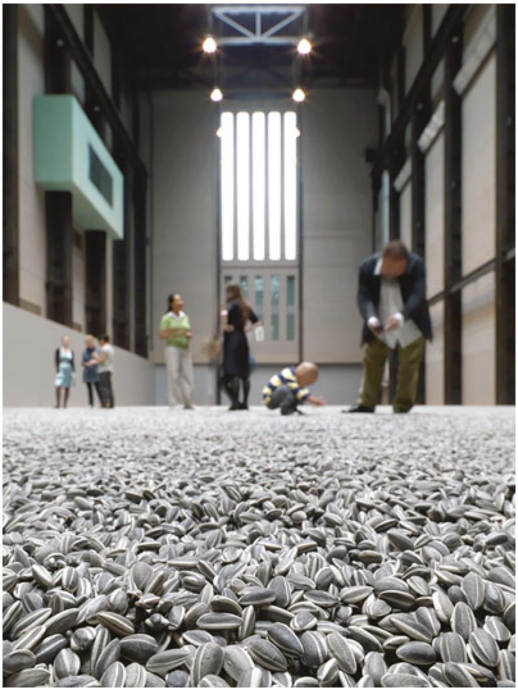

Fig. 8.1 Sunflower seeds by Ai Weiwei. Looking from a distance: an undifferentiated mass. Reprinted with permission from the copyright holders

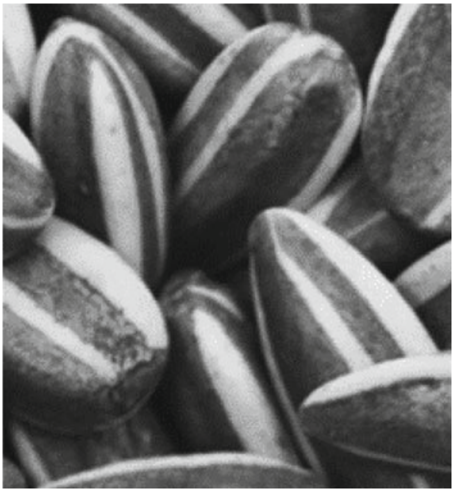

Fig. 8.2 Sunflower seeds by Ai Weiwei. Looking up close. Seeds with their own individuality. Reprinted with permission from the copyright holders

according to a range of diverse needs. “One size fits all” cannot be applied to this group. This will be one of the guiding principles underlining the approach to care which I describe in this chapter.

Within the uniqueness of each individual child, there are, however, features which allow us to group these children within the category of “gender identity disorder” according to the DSM-IV or “gender dysphoria in children,” as it will be called in the newer version of the classification. There has been a debate about whether or not to retain this presentation in DSM-V. The issues regarding classification are described in Chap. 7.

The term gender variance is generally used with reference to children who present features of atypical gender identity development, regardless of whether or not they present all the features of gender identity disorder (GID) or gender dysphoria (GD) in line with a recognized classification.

The question which arises is why these children and their family should be offered professional help. Because of the secrecy and shame in Western society surrounding these issues in the past, these children were not identified and professional help was not sought. Awareness about gender identity issues has increased since the appearance of the diagnosis of GID in the DSM-III classification in 1980, as well as through the action of the media. Families have therefore started to seek professional help. A number of services have developed and the rate of referrals has increased over the years (see Fig. 8.3 for referral trends in the UK).

Currently, the reasons for offering professional help include the following:

A number of these children experience distress due to the incongruence between their self-perception and the body. Because of their unusual presentation, some children are teased, bullied, or ostracized either in the family and/or in school. This may cause distress to the child and to the family. It affects well-being in the short and long term.

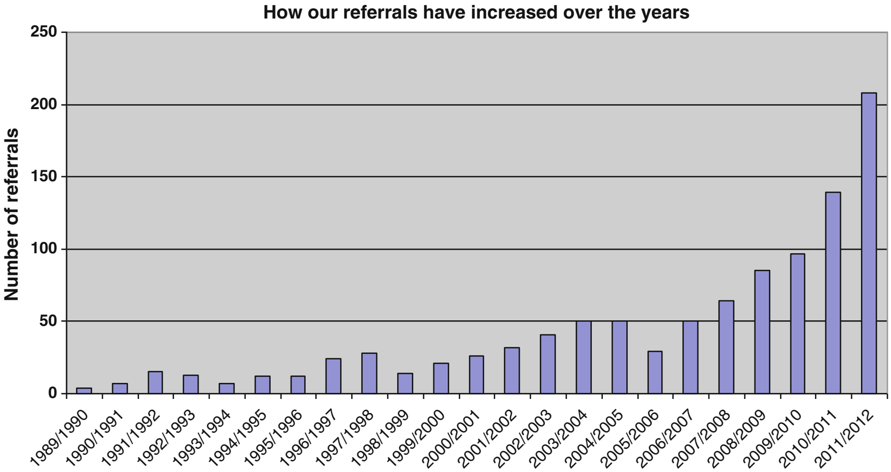

Fig. 8.3 Increase in referrals from 1989 to 2012 of the Gender Identity Development Service (GIDS) in London

A number of children present with associated psychological and social difficulties (see Chap. 9). Professional help is needed to explore whether or not there is a connection between gender dysphoria and the associated difficulties, and devise the appropriate form of help.

In addition, research shows that in only 10–30 % of prepubertal children with gender dysphoria, gender dysphoria persists into adolescence and beyond (Drummond, Bradley, Peterson-Badali, & Zucker, 2008; Green, 1987; Wallien & Cohen-Kettenis, 2008; Zucker & Bradley, 1995). Because of the variability of outcomes, some clinicians have defined their approach to care as "Watchful Waiting." Factors which may contribute to the persistence or desistence are unclear and a subject of current empirical research, although the intensity of GD, and a complete diagnosis of GD predicted persistence in one of the follow-up studies (Wallien & Cohen-Kettenis, 2008).

Professional interventions can help to alleviate the stress in the child and promote well-being. They can also assist the development of a child and observe the persistence or desistence of the gender dysphoria at the beginning of puberty. In a selected number of children, the distress brought about by pubertal changes can be alleviated by early pubertal suppression through the use of GnRH analogues (see Chap. 10). Therapeutic explorations in childhood can contribute to the process of better informed consent regarding the use of hypothalamic blockers at the beginning of the puberty.

The GIDS offers a multidisciplinary approach that ensures that all aspects of a child's development are taken into consideration, including the family and social contexts in which the child lives. Like the children we see, members of the professional team bring different clinical experience, skills, and personality within a common framework of professional values. This diversity adds to the richness of case discussion but also helps individual clinicians to reach, through discussions, a more balanced view regarding the best approach and interventions to the individual child and family.

8.2 Historical Background

The GIDS (or Gender Identity Development Clinic, as it was called at the time) started at St. George's Hospital, London, in 1989 following a workshop established in the mid-1980s (in which children and adolescents with gender identity disorder/variance were discussed). The service then transferred to the Tavistock and Portman NHS Foundation Trust in 1996 (Di Ceglie, 2002). From the beginning, links were established with two other services which existed at the time: the Gender Identity Service, Child, Youth, and Family Program currently at the Centre for Addiction and Mental Health in Toronto (which had been established in the mid-1970s) and the Gender Identity Clinic for Children and Adolescents established at the Utrecht University Medical Centre in 1987 and currently at the VU University Medical Center in Amsterdam, the Netherlands.

The models of clinical management developed in these two centers are extensively described by Zucker, Wood, Singh, and Bradley (2012) and by De Vries and Cohen-Kettenis (2012). Clinicians from these teams from London, Toronto, and the Netherlands and other professionals working in this field met at the first international conference on gender identity and development at St George's Hospital in London. This was the beginning of a series of debates continued in three further international conferences in 1996, 2000, and 2004 seeking to understand the gender dysphoria condition and the issue of clinical management. The models developed by the three services have a number of similarities, but also differences. It is beyond the scope of this chapter to attempt to describe them.

Following the international conference at London's Tavistock Centre in 1996, a group of clinicians drafted the guidelines for the management of GID in children and adolescents. These guidelines were eventually approved and published by the Royal College of Psychiatrists (1998). The guidelines emphasize the importance of adopting a developmental approach, the involvement of the family and the other social agencies as appropriate, and that care should be provided within a well-integrated, specialist multidisciplinary team. With regard to physical interventions, a distinction was introduced between reversible, partially reversible, and irreversible interventions, and a staged approach to management was proposed.

The guidelines were largely adopted by the Harry Benjamin International Gender Dysphoria Association (HBIGDA) Standards of Care (sixth version), in the section for children and adolescents (HBIGDA, 2001). In this sixth version, it was specified that the use of hypothalamic blockers should not occur before the young person has reached Tanner stage 2 of pubertal development (Tanner stages had not been taken into consideration in the Royal College guidance). The Standards of Care were recently reviewed and published by the World Professional Association for

Transgendered Health (WPATH; previously HBIGDA 2011). The American Academy of Child and Adolescent Psychiatry (AACAP) published a "Practice Parameter on Gay, Lesbian or Bisexual Sexual Orientation, Gender-Nonconformity, and Gender Discordance in Children and Adolescents." It suggests under principle 7 that "Clinicians should be aware of current evidence on the natural course of gender discordance and associated psychopathology in children and adolescents in choosing the treatment goals and modality" (AACAP, 2012).

In recent years, more specialist services for gender variant children and adolescents have been developed, especially in Western societies, and the numbers of referrals have increased in all three mentioned services.

8.3 Models of Care and Research Evidence

In the development of scientific knowledge, Kuhn put forward the theory of paradigms and "paradigm shift" (Kuhn, 1962). Atypical gender identity development within a simple paradigm would include only biological factors, whereas atypical gender identity development within a complex paradigm takes into consideration the influence and interaction between biological, psychological, and social factors. A "paradigm shift" in the area of sexuality occurred following the definition of the concept of gender identity in the early 1960s. Before 1955, there was no concept of gender identity, and the word gender was mainly confined to the domain of grammar. The only determinant of male and female was the body, and therefore, people for whom the perception did not match the appearance of their body could not articulate their experience with any clarity. In 1955, John Money introduced the concept of gender role. The term gender identity appeared in the early 1960s in association with the establishment of a gender identity study group at the University of California. Stoller (1992) defined it as:

> "*A complex system of beliefs about oneself: a sense of one's masculinity or femininity. It implies nothing about the origins of that sense (e.g. whether that person is male or female). It has, then, psychological connotations only: one's subjective state*" (p. 78).

Money (1994), in a paper on the history of gender identity disorder presented at a conference at St George's Hospital in London, concluded:

> "*In the second half of the 20th century … what did emerge was a new name for a new concept, gender identity, which brought about a reformulation in how we think about sex and its disorders. This reformulation diffused far beyond the confines of medicine, where it began, and permeated the policies and politics of sex in society at large. It did so to such an extent that the social history of our era cannot be written without naming gender, gender role and gender identity as organizing principles*" (Money, 1994, p. 176).

What has occurred is a sort of Copernican revolution in the field of sexuality. Before Copernicus, previous literature and common sense seemed to suggest that the sun revolved around the Earth and Galileo, who supported Copernicus' view that the Earth revolved around the sun, had to abjure his beliefs to save himself. Similarly, before the definition of the concept of gender identity, the determinants of our gender were only the physical appearance of the body, as common sense would suggest. However, we now also have to consider our own mental perceptions, i.e., our experience of gender identity embedded in brain functioning. In the last two or three decades, neuroscientific research has attempted to establish the contribution of brain function to the development of gender identity in interaction with individual early experience in the course of development. As yet, we do not have a satisfactory understanding of gender identity development or of the interaction between brain functioning, hormones, and experience (see Chap. 3).

8.4 Gender Identity Development Service

Following the definition of gender identity in the 1960s, gender identity disorder in 1980, and the development of services for children and adolescents in the 1980s, a number of guidelines for the management of the condition were published (see Sect. 8.2). However, the research evidence is still poor to date. The report of the American Psychiatric Association Task Force on Treatment of GID states that "the highest level of evidence available for treatment recommendations for these children can best be characterized as expert opinion" (Byne et al., 2012).

Our model of management at the Tavistock and Portman NHS Foundation Trust is based on the understanding of atypical gender identity development within a complex paradigm. It has been informed by the fact that the causation of the phenomenon of GID remains unclear and it is probably multifactorial. It is also influenced by current cultural values and societal attitudes regarding the development of gender identity. Our therapeutic experience has shown that children are very sensitive and feel easily intruded upon by anyone attempting to change who they feel they are and by those who minimize their feelings. Therefore, at the Gender Identity Development Service, we have developed a model of management in which altering an individual's perceived gender identity is not a primary therapeutic objective. Instead, emphasis is placed on the following list of therapeutic aims (Di Ceglie, 1998). The primary therapeutic aims are:

- To foster recognition and nonjudgmental acceptance of gender identity problems.
- To ameliorate associated behavioral, emotional, and relationship difficulties.
- To break the cycle of secrecy.
- To activate interest and curiosity by exploring the impediments to them.
- To encourage exploration of the mind–body relationship by promoting close collaboration among professionals in different specialties, including pediatric endocrinology.

- To allow mourning processes to occur.
- To enable symbol formation and symbolic thinking.
- To promote separation and differentiation.
- To enable the child or adolescent and the family to tolerate uncertainty in gender identity development.
- To sustain hope.

It is important to add to this list the need to combat **stigma** which is often associated with the experience of atypical gender identity and is at times internalized by the individual experiencing GID. It is also valuable to alleviate the feeling of **shame** that some children/adolescents and their families experience and enable people to develop skills in handling social interactions and dealing with possible hostility.

In the report by the American Psychiatric Association (Byne et al., 2012), approaches to working with children with GID were classified in three groups.

> "*The first of these focuses on working with the child and caregivers to lessen gender dysphoria and to decrease cross-gender behaviors and identification… A second approach makes no direct effort to lessen gender dysphoria or gender atypical behaviours… The goal is to allow the developmental trajectory of gender identity to unfold naturally without pursuing or encouraging a specific outcome… A third approach may entail affirmation of the child's cross gender identification by mental health professionals and family members*."

The authors critically review these three approaches. The GIDS approach I have described above comprises elements of the second and third approach as it has exploratory and affirmative elements.

In our service, we describe the process of care for children with gender dysphoria in three components: referrals, assessment, and therapeutic help or treatment.

8.4.1 Referrals

The GIDS in London offers a nationwide service to young people aged up to 18 years. Referrals are accepted from a wide range of professionals in health, social services, and education departments who have concerns about a young person's gender development and associated difficulties. We encourage referrers to discuss the referral with the family and seek their agreement.

Since the service cannot respond to emergencies or offer treatment to associated psychological and psychiatric problems (e.g., school refusal and compulsive symptoms), we require, in the majority of cases, that the young person's case is also open to local Child and Adolescent Mental Health Services (CAMHS). The service will undertake joint work, consultation, and liaison with the local CAMHS team and responsible professional network. The graph below (see Fig. 8.3) shows the increase in referrals from the start of the service in 1989 to date.

8.4.2 The Network Model

Collaboration between the Gender Identity Development Service and local services begins at the time of referral, by ensuring that local professionals involved with a child or young person continue to be involved. This aims at containing complex interaction within the family and professional network and facilitating the management of gender dysphoria. We call this the network model of management. Following a referral, an assessment of the child and family will be offered. This will be followed by a professional outreach meeting arranged locally and including local professionals involved in the case as well as one or two members of the GIDS team traveling to various parts of the country. The aim of the meeting is to clarify tasks, roles, and facilitate communication between agencies and to agree on a shared management plan. In other cases, a professional network meeting is offered first and a specialist assessment follows, when appropriate. The management plan agreed to and the progress made is reviewed at the follow-up network meeting held at regular intervals, e.g., once a term or twice a year.

The clinical team has found the following framework helpful in conducting these network meetings; these will start with a brief professional meeting in which people introduce themselves and describe their role in the case and the work undertaken since the previous meeting, or if this is the first meeting, the work undertaken to date. This leads to an agenda of relevant issues being established. It is useful to have a brief professional meeting before involving the family as the work is better coordinated when the professionals have an opportunity to assimilate each other's practices. The young person and the family then join the meeting. After introductions, a summary of the issues discussed is given, and a discussion with the adolescent and family follows. Usually a local professional chairs the meeting. A member of the GIDS team proposes this framework at the beginning of the meeting.

Through this collaborative work, a holistic approach is offered in response to the different needs of the child and the family. Good communication and integration among the various professionals is essential in this respect. In some cases, the dynamics in the individual child or the family are mirrored by the professional network, as described by Britton (1981). When this occurs, an examination of these dynamics among the staff provides a useful understanding of the dynamics within the child and family (Di Ceglie, 2008).

Network meetings are particularly useful to make preparations for the transition of the child with gender dysphoria from primary school to secondary school, which in the UK occurs at the age of 11. This can be fraught with difficulties, as the child will move to a bigger environment and will have new peers and new teachers. Professional network meetings involving the current teachers and the prospective teachers should be arranged in good time before the transition occurs. The meeting allows the new staff group to learn from the experience of the previous teachers and to take on board the specific needs of each individual child and family. This, in turn, will enable the new staff to respond appropriately to these needs, through a process of mutual negotiation.

8.4.3 Assessment and Therapeutic Work with Children

We use the term assessment, in preference to other terms such as "diagnostic procedure," as it best reflects the atmosphere and professional attitude we wish to create. The Oxford Dictionary describes the word "assessor" as "a person who sits beside another, who shares another position." We also use the words "therapy and therapeutic" as all our interventions aim at promoting well-being and are sensitive to the needs of the child and the family.

Another important aspect in the assessment, which is common to all clinical assessments, is the capacity of the therapist to orient himself or herself toward the psychological needs of the child and the family. In some cases, this can be achieved by adopting a language which is concrete enough to be understood by the child (maybe with the help of the parents) or by using play and drawings as a form of communication. Another example of the therapist's orientation toward the child/family is the ability to be in touch with the child/family anxieties about attending an interview at GIDS, such as the fear of being judged unfavorably or of being in a strange place with strange people. Verbalizing these fears can facilitate trust and therefore engagement with the therapist and the service. For a detailed description of the process of orientation, see Di Ceglie (2013).

The approaches to assessment in the Netherlands and Canada are described in detail by De Vries and Cohen-Kettenis (2012) and Zucker et al. (2012).

At GIDS children will be initially assessed together with the family or with their caregivers for about four sessions. In order to ascertain the features of a GID, it is important to facilitate communication about the young person's behaviors and perceptions regarding his or her gender identity with the family. When this is not possible, we will meet with the parents separately. All assessments will consider whether or not the child presents with the diagnostic features of a gender identity disorder or gender dysphoria. These include identity statements, cross-dressing, toy and role play, peer relations, mannerisms and voice, anatomic dysphoria, and rough-and-tumble play (Zucker & Bradley, 1995).

The assessment will ascertain whether or not the child fulfills all the criteria for GID and the presence of coexisting psychosocial difficulties. During the assessment, attention is paid to the quality of relationships within the family and that between the young person and the parents. Attention is also paid to whether or not there are other psychosocial difficulties in other members of the family as well as the attitude of the parents to the gender-dysphoric feelings and cross-gender behaviors.

There is also an evaluation of the risk of self-harm. In our service, an audit has shown that prior to referral, 7 % of gender-dysphoric children show self-harming behavior and that the risk increases considerably between the age of 12 and 15 and decreases after this. The overall risk of self-harm is lower following attendance at GIDS (Skagerberg et al., 2013).

At the first assessment meeting, the family is required to complete a series of questionnaires. To assess GID or gender dysphoria for the prepubertal group, the service devised a questionnaire based on the DSM criteria; one for the parents and one for the child. Another questionnaire evaluates parental attitudes toward the child's atypical gender development. The child behavior checklist (Achenbach, 2001) is used to evaluate the associated psychosocial difficulties and the social responsiveness scale (SRS) to evaluate social interactions linked to autistic spectrum conditions (Constantino, 2005).

If there are concerns about a child's mental health, then the local service will be asked to provide further psychiatric and multidisciplinary input. Child psychotherapy is considered in a small number of cases in which there are considerable associated psychological difficulties, such as OCD, symptoms of severe anxiety, and autistic spectrum features. This will require individual assessment sessions. Psychotherapy is usually offered by local services. In some cases, it may be necessary to conduct a range of further assessments of various forms, such as psychological testing for other conditions.

The outcome of the assessment will establish the presence of diagnostic criteria for gender dysphoria and whether or not there are other associated psychosocial difficulties, as well as the families' ability to communicate and support the child. According to the needs of the child, it may then recommend therapeutic exploration with the family, child psychotherapy/counseling and parental support/counseling, consultation to the network with or without further direct involvement with the young person and his or her family, intermittent reviews to monitor gender identity development (two or three times a year), group work for parents, occasionally a referral to the pediatric liaison clinic for physical assessment, or a combination of the above.

8.4.3.1 Psychotherapeutic Approach

The therapeutic aims described above are used in a flexible way within the different therapeutic modalities to orientate the therapist in the exploration. Some aims are more relevant than others in particular situations. A clinical vignette illustrates this point:

James

James, a natal male, was referred to the Gender Identity Development Service at the Tavistock Centre London at the age of 8 years. At the assessment interviews he said that he wished at times he was a girl. He had been secretly dressing up in his mother's clothes. He liked to play with dolls and cuddly toys and fantasized that he was a mother feeding them. He played 'weddings' and liked to be in the role of the *bride. At school he wanted to play with girls and avoided rough-and-tumble play or other activities with boys. His maternal grandmother had looked after him from age 3 months to 5 years, as his mother was often away for her work. The grandmother involved him in many activities, including cooking and tidying up the house. After her sudden death in hospital, James developed features of gender dysphoria. He could not talk about the loss of his grandmother or even mention her, but he concretely identified with her and persistently wished to continue with all the activities in exactly the same way as he had once done with her. The therapeutic exploration with the family, focusing on a family tree constructed over many sessions, allowed him to describe these experiences he had with his grandmother and allowed him to put these into words. This was facilitated by the therapist. His female identification gradually reduced in intensity and eventually disappeared.*

In this case the psychological work focused not only on mourning processes, but it also removed the secrecy about his gender problem, encouraged curiosity about its origins and established a link between his atypical gender development and the way he had coped with the loss of his grandmother. The capacity for mental representation was stimulated, so that he could have a mental picture of her and memories of the past, rather than concretely identifying with and becoming her. The processes involved in this case are described in more detail in 'A Stranger in My Own Body: Atypical Gender Identity Development and Mental Health' (Di Ceglie, 1998*). In this case the primary aims which oriented the therapeutic exploration included breaking the cycle of secrecy, facilitating mourning processes, and enabling symbolic thinking.*

In some cases, other psychological conditions may coexist with gender dysphoria. Recent research has highlighted the co-occurrence of gender dysphoria and autistic spectrum conditions in some children (De Vries, Noens, Cohen-Kettenis, van Berckelaer-Onnes, & Doreleijers, 2010). When the assessment shows the presence of autistic spectrum features, it becomes important to work toward amelioration of the associated behavioral, emotional, and relationship difficulties affected by the condition. Promoting curiosity, symbolic thinking, and tolerance of uncertainty become other aims to be pursued. If empathy is affected, as shown in interviews and a low empathy score in questionnaires, this should also be addressed.

In the work with families, one way of enhancing empathy in the child could be the joint construction of a family tree, which focuses on highlighting intersubjective experiences. The child and other members of the family are asked to imagine how other members of the family, who do not know the presence of gender dysphoria in the child, would react to becoming aware of it. How other relatives would understand it and what their emotional response would be are key elements in this process. This would address the cognitive and affective components of empathy (Baron-Cohen, 2008, p. 62). The mutual expression of different perceptions of family members could expand the child's awareness of the presence of multi-representations and his or her capacity to accept diversity. This process can be extended to other members of the child's peer group and social network. It is hoped that the repetition of this and other similar types of interventions will increase the capacity in the child for empathic thinking. These exploratory interventions can also pave the way to better informed consent about possible treatment choices during puberty, if appropriate.

GIDS can offer pubertal suppression, through the use of GnRH analogues, to children in whom the gender dysphoria persists into adolescence. This intervention has been offered within a research protocol since 2011. The protocol was drafted following a wide debate involving service users, professionals, and relevant professional organizations, such as the British Society for Paediatric Endocrinology and Diabetes (BSPED, 2009). It received ethical approval and has a well-established system of informed consent from young people and their parents/caregivers. It adopted the eligibility criteria similar to those of the Center of Expertise on Gender Dysphoria in Amsterdam (Delemarre-van de Waal & Cohen-Kettenis, 2006; De Vries, Cohen-Kettenis, & Delamarre-van de Waal, 2007). The eligibility criteria used by GIDS are described in Box 8.1.

For further information regarding hormonal management in adolescents, see Chap. 10.

8.5 Gender Variant Role Expression in Childhood

8.5.1 Presentation of Gender Variant Role Expression

This section deals with the question: Should prepubertal children be allowed to live in their perceived gender? I will start with a quote from the book “Why Be Happy When You Could Be Normal?” (Jeanette Winterson, 2011):

> *“Jeanette had been talking with her adoptive mother about her relationship with another girl. Then her mother asks:*
>
> *‘Jeanette, will you tell me why?’*
>
> *‘What why?’*
>
> *‘You know what why…’*
>
> *But I don’t know why… what I am… why I don’t please her. What she wants. Why I am not what she wants. What I want or why. But there is something I know: ‘When I am with her I am happy. Just happy.’*
>
> *She nodded. She seemed to understand and I thought, really, for that second, that she would be on the same side of the glass wall. I waited.*
>
> *She said: ‘Why be happy when you could be normal?’”*

This quote shows a parental attitude influenced by perceived social norms and, perhaps religious beliefs, in contrast with a wish for self-expression and emotional well-being. In our society, repression of one’s own feelings and emotions not only is no longer seen as valuable but is considered as contributing to psychological difficulties and affecting mental well-being negatively. With regard to children with gender dysphoria who identify with the other sex, the expression of these

Box 8.1 Eligibility criteria for pubertal suppression

Eligibility criteria (Delemarre-van de Waal & Cohen-Kettenis, 2006)

A. Psychological criteria

Before the adolescent can be considered for inclusion in the research protocol, s/he should have been seen by the service at the Tavistock clinic site for at least 6 months and should have attended at least four interviews for assessment and therapeutic exploration of their gender identity development:

1. Standard readiness criteria relating to psychological stability sufficient to withstand the stresses of sex reassignment.
2. Fulfills the following criteria relating to GID:
   (a) Throughout childhood (defined as over 5 years), the adolescent has demonstrated an intense pattern of cross-gendered behaviors and cross-gender identity.
   (b) The adolescent has gender dysphoria that is significantly increased with the onset of puberty. Following assessment the clinician(s) working with the young person deems that there is a high likelihood of the young person experiencing severe psychological distress consequent on experiencing full pubertal development before the blocker is implemented.
3. The young person and parents/guardians are actively requesting blockers.
4. The young person is able to give informed consent.

B. Physical/medical criteria

1. In established puberty:
   - For biological males, Tanner (genital and pubic hair (PH)) stage 3 and above
   - For biological females, Tanner (breast and PH) stage 2 and above

   Note that these pubertal criteria match those used by the Dutch. The rationale for the sex difference is that the pubertal growth spurt which early intervention aims to avoid occurs earlier in females (Tanner 2–3) than in males (Tanner 3–4); thus, earlier intervention is required in females but is not necessary in males to avoid unwanted growth (in males) or growth termination (in females).
2. Normal endocrine function and karyotype consistent with biological sex. Note that the presence of mild elevations of androgens in biological females consistent with polycystic ovarian syndrome is not an exclusion criterion.
3. Age 12 and above (Delemarre-van de Waal & Cohen-Kettenis, 2006).

perceptions in the social context has raised a number of controversies and caught the attention of the media in the UK and abroad.

A case vignette from the 1990s illustrates how a family dealt with gender role expression in a child and what our professional role was in assisting the family.

Case Vignette: Martin

The Referral. Martin was referred in the early 1990s to the Gender Identity Development Service at the age of 8 when he was attending a primary school in Barnet, London.

The educational psychologist reported the mother saying that he had told her when he was 7 that he wanted to be a woman when he grew up. He enjoyed dressing in women's clothing and, since he could walk, he liked to wear high heels and used tea towels to mimic long hair. He was very fond of barbie dolls and his mannerisms and style of walking were feminine. At school, he played only with girls. He lacked confidence and was teased by other children, who called him "poof" and "queer." He suffered from symptoms of anxiety, including stomach upsets, dizziness, and headaches. His mother did not encourage his feminine behavior, but was supportive.

Assessment and Management. At the GIDS we confirmed that Martin presented with the features of a very well-established gender identity disorder (DSM-IV). His anxiety about attending school resulted in poor attendance, and he also experienced teasing on the estate where he lived. He also had difficulties separating from his mother. At our service, we started to work closely with the family which consisted of Martin, his mother, and his stepfather, and we had meetings with the school staff to facilitate his attendance at school. The network model proved helpful in managing this issue.

Further Developments. Two years later Martin moved with his family to Brighton. Here his wish to live in a female role became very intense and the parents agreed to let him live as a girl, by dressing in female clothes and changing his name to Martina.

In Brighton, Martina became involved in individual therapeutic work with a community nurse in the local CAMHS. A colleague and I continued to see the parents every 2 months to help them to reflect on the gender identity and other developmental issues involved and to make more informed decisions with their child (parental counseling). The parents attended a group for parents of children with gender dysphoria for 6 months, as part of the therapeutic program (Di Ceglie & Coates, 2006). We continued to hold regular network meetings, including the school staff, in Brighton two or three times a year. Martina attended a small special educational unit in female role following careful preparation and discussions of the issues involved between the professional network (including us) and the family.

Child Protection. When Martina was 13, a child protection conference was called as the education department had become concerned that the GID problem could have been created by parental attitude. After an investigation and a child protection conference, no child protection issues were found. As a result of this conference, the mother was offered further supportive individual counseling by local services.

Unexpected Outcome. When Martina was 14, while waiting to be seen by our pediatric endocrinologist as she was entering puberty, she unexpectedly announced to her mother that she no longer wished to be a girl, and she now felt happier about being a boy. From then, Martina reverted to living as Martin.

The next time I saw Martin, he had physically developed a lot and had the clear appearance of a boy. At the last professional/family network meeting, I asked Martin if he thought that his parents had made a wrong decision in allowing him to attend school in a female role and he replied without hesitation that it had been right because that was how he had felt at the time.

The following observations can be drawn from this clinical experience.

Pubertal development can sometimes, even in well-established cases of gender dysphoria in childhood, change the course of gender identity development, in line with recent research on "desisting and persisting gender dysphoria after childhood" (Steensma, Biemond, de Boer, & Cohen-Kettenis, 2011).

A parental response which goes along with the intense wishes of the child to live in the perceived gender identity and role does not necessarily influence the course of gender identity development. However, maintaining an open mind and a reflective attitude facilitates the process of change, if this occurs.

Our professional role was to maintain a reflective approach in working with the family and the professional network, to assist the family in evaluating pros and cons, and to facilitate decision making within the family and school staff regarding what was in the best interests of the child in that particular social context.

8.5.2 Research Evidence

As mentioned earlier, long-term follow-up studies have shown that only in a small proportion of prepubertal children presenting with the features of a gender identity disorder did the gender dysphoria persist through adolescence and beyond. There is no empirical and systematic research on the outcome of allowing gender role expression in line with their perceived gender identity in children and therefore no evidence to suggest which approach is best.

Steensma et al. (2011) suggest that young people who changed their perceived gender identity:

> "*considered the period between 10 and 13 years of age to be crucial…Both persisters and desisters stated that the changes in their social environment, the anticipated and actual feminization or masculinization of their bodies, and their first experiences of falling in love and sexual attraction had influenced their gender related interest and behavior, feelings of gender discomfort and gender identification.*"

Box 8.2 Social transition in childhood: some points from the WPATH Standards of Care (2011)

Families vary in the extent to which they allow their young children to make a social transition to another gender role. Social transitions in early childhood do occur within some families with early success. This is a controversial issue, and divergent views are held by health professionals.

Mental health professionals can help families to make decisions regarding the timing and process of any gender role changes for their young children.

A change back to the original gender role can be highly distressing and even result in postponement of this second social transition on the child's part (Steensma & Cohen-Kettenis, 2011)

Mental health professionals can assist parents in identifying potential in-between solutions or compromises (e.g., only when on vacation). It is also important that parents explicitly let the child know that there is a way back.

Regardless of a family's decisions regarding transition (timing, extent), professionals should counsel and support them as they work through the options and implications.

Steensma and Cohen-Kettenis (2011) also report that gender role transition in childhood has more frequently been observed in the Netherlands in recent years. They state that in a group of young people with gender dysphoria in childhood who had desisted, "two girls, who had transitioned when they were in elementary school, reported that they had been struggling with the desire to return to their original gender role, once they realised that they no longer wanted to live in the 'other' gender role. Fear of teasing and shame to admit that they had been 'wrong' resulted in a prolonged period of distress". The WPATH Standards of Care (2011) takes into account the various experiences reported about social transition and offers a balanced view and guidance to professionals and families (see Box 8.2).

Given the lack of research evidence, my initial thinking about the management of gender role and social transition in childhood was based on a long-term observation of the case described from the 1990s.

Since then I have seen a number of prepubertal children, but these experiences have not led to me changing my initial views about social transition. Some of these children have continued to live in their natal gender, while others have not. It is possible that gender role transition in childhood, without a concomitant reflective practice and awareness about the possibility of change, could influence decision about pubertal suppression and make it more difficult to return to the natal gender role.

I am very interested to find out about other experiences, particularly those different from the one I have described. Obviously more observation and research evidence is needed in this controversial area and I believe that there should always be room for changing views as new evidence emerges.

8.6 Conclusion

I have presented a model of care based on a framework which integrates psychodynamic, biological, and psychosocial aspects and is sensitive to current cultural attitudes in the UK. No doubt, the complex paradigm regarding atypical gender identity development will shift as clinical and research evidence progresses and the social context changes. New language and nomenclature will emerge.

Consequently, models of care will change with new approaches being developed. I believe, however, that the trend toward ensuring greater equality of care for the diverse needs of these children will continue. With increased numbers of immigrant families and the development of more culturally diverse societies, different systems of cultural and religious beliefs about atypical gender identity will also influence the debate about equality. This will require a great deal of negotiation among the organizations and services dealing with children with gender dysphoria and their families.

Case descriptions are anonymous and names and places were changed for confidentiality.

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Chapter 9
Models of Psychopathology in Children and Adolescents with Gender Dysphoria

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Abstract This chapter reviews empirical data on the extent to which children and adolescents with gender dysphoria show other types of psychopathology or behavior problems. It then reviews several models that have attempted to account for this psychopathology when it is present. Several factors have been reasonably established as accounting for at least some of the variance in general psychopathology, including peer social ostracism, cultural factors, and generic risk factors for psychopathology in the family. Surprisingly, little empirical attention has been given to the possibility that gender dysphoria is inherently distressing and thus is another source of the socioemotional problems that children and adolescents with this diagnosis experience.

9.1 Introduction

In this chapter, we will provide a summary of the empirical literature regarding the presence (or absence) of psychopathology in children and adolescents with gender dysphoria (GD), the DSM-5 diagnostic term that has replaced the DSM-IV diagnostic label of gender identity disorder (GID) (American Psychiatric Association, 2013). We will first focus on a specific question: Do children and adolescents with GD show, on average, "other" types of psychopathology? After summarizing the data that have addressed this question, we will review several models of psychopathology that have attempted to articulate why there might be, at least in some children and adolescents with GD, the presence of other types of psychopathology or

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behavioral and emotional problems.[1] We will not discuss the corresponding literature on adults with GD, as this is considered elsewhere in this volume (see Chap. 13; see also Lawrence & Zucker, 2012).

9.2 Methods of Assessment

In the empirical literature on children and adolescents with GD, several assessment approaches have attempted to ascertain the presence (or absence) of various forms of psychopathology: (1) clinical chart reviews, (2) standardized questionnaires, (3) diagnostic interview schedules, and (4) indices of emotional impairment or assessment of personality functioning and structure on projective tests. Because descriptive material from chart review studies typically lacks a standardized methodology, we will not summarize this literature (e.g., Di Ceglie, Freedman, McPherson, & Richardson, 2002; Rosenberg, 2002; Spack et al., 2012) although it has the potential to be informative in identifying domains for more systematic approaches. Rather, we will focus on samples of children and adolescents with GD that have relied on standardized questionnaires of behavioral and emotional problems, diagnostic interview schedules, projective testing, and item-specific analyses.

9.2.1 Standardized Questionnaires

The most systematic information on general behavioral and emotional problems in children and adolescents with GD has relied on standardized questionnaires, most typically the Child Behavior Checklist (CBCL), the Teacher's Report Form (TRF), and the Youth Self-Report (YSR) Form, which are now part of a family of forms known as the Achenbach System of Empirically Based Assessment (ASEBA) (Achenbach & Rescorla, 2001; see also Rekers & Morey, 1989). The advantage of this assessment method is that it covers a broad age range, has well-established norms, allows the use of multiple informants, and has been validated in many different countries and across a variety of cultural groups. Factor analysis of these questionnaires has identified both narrow-band and broad-band factors of psychopathology: The two broad-band factors have been termed internalizing and externalizing, respectively.

Table 9.1 summarizes CBCL, TRF, and YSR data as a function of sex, age range, and clinic site. Because this review is not meant to be exhaustive, we used as a simple metric the percentage of patients whose total behavior problem score fell in the clinical range (>90th percentile).

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[1] By models of psychopathology, we are not referring to the theoretical and philosophical discourse on whether or not GD per se is a type of psychopathology warranting classification as a psychiatric disorder. On this point, Meyer-Bahlburg (2010) provided a detailed analysis of the issue during the literature review phase of the DSM-5 process.

Table 9.1 Summary of Child Behavior Checklist, Teacher's Report Form, and Youth Self-Report Form studies of children and adolescents with gender dysphoria

Study and measure	*N*	Sex	Age range	Site	Clinical range (in %)
Child Behavior Checklist					
Coates and Person (1985)	25	M	5–12	New York	84
Cohen-Kettenis, Owen, Kaijser, Bradley, and Zucker (2003)	97	M	4–12	Utrecht	59.3
	33	F	4–12	Utrecht	
	305	M	3–12	Toronto	47.2
	53	F	3–12	Toronto	
Hill, Menvielle, Sica, and Johnson (2010)	10		4–5	Washington, DC	20.0
	16		6–12	Washington, DC	12.5
Singh, Bradley, and Zucker (2011)	139		4–5	Toronto	23.0
	131		6–12	Toronto	60.1
Cohen-Kettenis and van Goozen (2002)	11	M	11–17	Utrecht	27.2
	18	F	11–18	Utrecht	33.3
de Vries, Doreleijers, Steensma, and Cohen-Kettenis (2011)	29	M	11–16	Amsterdam	34.5
	35	F	11–17	Amsterdam	54.3
Zucker et al. (2012)	83	M	13–20	Toronto	81.9
	71	F	13–21	Toronto	76.1
Teacher's Report Form					
Steensma, Zucker, Kreukels, and Cohen-Kettenis (2012)	164	M	5–11	Amsterdam	27.4
	78	F	5–11	Amsterdam	25.6
	259	M	5–11	Toronto	35.5
	53	F	5–11	Toronto	45.3
	45	M	12–18	Amsterdam	33.3
	45	F	12–18	Amsterdam	33.3
	41	M	12–18	Toronto	53.7
	43	F	12–18	Toronto	60.5
Youth Self-Report					
de Vries, Doreleijers et al. (2011)	27	M	11–16	Amsterdam	25.9
	31	F	11–17	Amsterdam	29.0
Di Ceglie (2012)	57	M	12–18	London, UK	47.4
	84	F	12–18	London, UK	48.8
Zucker et al. (2012)	81	M	13–20	Toronto	44.4
	72	F	13–21	Toronto	37.5

Note. In Cohen-Kettenis et al. (2003), CBCL data were available for 123 patients from Utrecht and 343 patients from Toronto. Unfortunately, the clinical range scores were not reported separately by patient's sex. The CBCL data from Toronto supersede an earlier summary by Zucker and Bradley (1995, pp. 79–83, 94–98), so these data are not reported here. In Singh et al. (2011), patients (250 boys, 20 girls) were matched for social class with the patients from Hill et al. (2010). Some of these patients were reported on in Cohen-Kettenis et al. (2003). The Hill et al. data reported on in the table were extracted from a total sample of 22 boys and 7 girls. The Cohen-Kettenis et al. (2003) and Zucker et al. (2012) data supersede an earlier report (Zucker, Owen, Bradley, & Ameeriar, 2002), which is not included here. Clinical range data from de Vries, Doreleijers et al. (2011) for both the CBCL and YSR provided by A. L. C. de Vries (personal communication, December 4, 2012). The TRF data in Steensma et al. (2012) supersede a preliminary report from Zucker and Bradley (1995, pp. 83–86) on the Toronto sample, so these data are not reported here

On the CBCL, it can be seen that, across studies, there was considerable variability in the percentage of clinical range cases: from a low of 12.5 % of 6- to 12-year-old children reported on by Hill et al. (2010) to a high of 84 % of 5–12-year-old boys reported on by Coates and Person (1985).[2] To make some sense of these data, it is helpful to know the percentage of clinical range cases for children and youth in the CBCL standardization sample. From Achenbach and Edelbrock (1983), we know that about 9–12 % of non-referred children and adolescents have clinical range scores and that about 71–77 % of referred children and adolescents have clinical range scores. Thus, in most of the samples summarized in Table 9.1, the CBCL data more closely approximated that of referred children and adolescents than non-referred children and adolescents in the standardization sample.

Only one study utilized TRF data (Steensma et al., 2012). About 9 % of non-referred children and adolescents have clinical range scores on the TRF, and the corresponding percentage for referred children and adolescents is about 47–50 % (Achenbach & Edelbrock, 1986). It can be seen from Table 9.1 that the children and adolescents from the Toronto clinic had TRF scores that were fairly similar to the referred sample in the standardization study, whereas the Dutch children and adolescents had TRF scores intermediate between the non-referred and referred standardization samples.

On the YSR, about 9–12 % of non-referred youth have clinical range scores, whereas 30 % of referred boys and 40 % of referred girls have clinical range scores (Achenbach & Edelbrock, 1987). The three YSR studies reported on in Table 9.1 suggest clinical range scores for GD adolescents that approximated that of the referred youth in the standardization sample.

The CBCL, TRF, and YSR data sets have yielded two other consistent findings: an age-related increase in the number of behavior problems and a pattern of higher internalizing than externalizing problems in GD males whereas this pattern has been less consistent in GD females; in some of the studies, there was no significant difference between internalizing and externalizing scores for GD females (see Zucker, 2005a, 2005b), but, in others, internalizing problems predominated (see Steensma et al., 2012).

In taking stock of the empirical database, two basic methodological issues should be considered: (1) Was the sample representative of the clinical population from which it was drawn? (2) What do we know about cross-informant agreement?

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[2] The CBCL and the YSR have two specific items pertaining to cross-gender behavior: “Behaves like opposite sex” or “I act like the opposite sex” (Item 5) and “Wishes to be of opposite sex” or “I wish I were of the opposite sex” (Item 110). The TRF has only the corresponding Item 5. In addition to these items, it is not unusual for parents to endorse other items on the CBCL that reflect cross-gender identification. For example, a parent might endorse “Strange ideas” (Item 85) and then provide an example such as “He wants to die and come back as a girl.” Youth may also make reference to gender issues on certain YSR items. In most of the studies reported on in Table 9.1, these items were scored as 0 to avoid any artificial inflation of the general behavioral disturbance indices. In Coates and Person (1985), however, it is unlikely that this procedure was followed. Thus, their percentage of clinical range cases may have been somewhat elevated because of this.

Regarding the first question, the Dutch group and our own group have been relatively successful in obtaining CBCL, TRF, and YSR data on consecutive referrals (e.g., Cohen-Kettenis et al., 2003; Steensma et al., 2012; Zucker et al., 2012). This has been particularly so for the larger N studies using the CBCL and the YSR. A somewhat greater percentage of children and youth did not have TRF data available: Some parents did not want the teacher to complete the TRF for privacy reasons, some adolescents had dropped out of school, etc. However, Steensma et al. (2012) did a careful internal validity check on their data set, which suggested that the available TRF data were reasonably representative of the entire sample. The de Vries, Doreleijers et al. (2011) study was limited only to GD adolescents deemed eligible for puberty suppression treatment. Since CBCL and YSR data were not provided for GD adolescents not deemed eligible for this biomedical treatment, it is not known if the latter group was similar to or different from the patients who were recommended to receive this treatment. Zucker et al. (2011) did not find significant differences in clinical range scores on the CBCL or the YSR between adolescents recommended and not recommended for puberty-blocking treatment; however, on the YSR, the latter group had a significantly higher sum score than the former group.

Hill et al.'s (2010) sample had the lowest percentage of CBCL scores in the clinical range. Apart from the small sample size, it is important to consider some other methodological issues in that study. Singh et al. (2011) noted that the parent participants did not represent consecutive referrals to the Children's Sexuality Advocacy and Education Program, housed at the Children's National Medical Center in Washington, DC. Rather, the sample was composed of "those parents who consented to participate in the research" (Hill et al., 2010) and the participation rate was not provided. Second, the time at which parents participated in the study varied (some were evaluated at baseline, but others had been involved in the program for unspecified lengths of time). Third, Hill et al. reported that 52 % of the children in their sample were adopted, which is an astonishingly high rate and certainly higher than the rate reported on from the Toronto clinic (Zucker & Bradley, 1998). Lastly, it was noted that the Hill et al. participants were largely from families from a higher social class background. Singh et al. (2011) attempted to provide a more careful comparative analysis that matched for social class background. When matched for age range and social class, there were both similarities and differences between Hill et al. and Singh et al. On the one hand, the percentage of clinical range scores for children 4–5 years of age was similar (20.0 % vs. 23.0 %), but for children 6–12 years of age, there was a substantial difference (12.5 % vs. 60.1 %).

Regarding the second question, it has long been recognized that cross-informant agreement on the CBCL, TRF, and YSR can be quite variable (Achenbach, McConaughy, & Howell, 1987; Duhig, Renk, Epstein, & Phares, 2000). In Cohen-Kettenis et al. (2003), mother–father correlations were available from the Toronto clinic patients. Across three indices of CBCL behavior problems, interparent correlations ranged from 0.50 to 0.61 (all ps $<$ 0.001). In Zucker and Bradley (1995), CBCL-TRF correlations ranged from 0.40 to 0.63 (all ps $<$ 0.001) for 46 boys for whom both measures were available. In Zucker et al. (2012), CBCL-YSR correlations were statistically significant for female adolescents with GD (rs ranged from

0.44 to 0.48, all $ps < 0.001$); however, for male adolescents with GD, only one of the three correlations was statistically significant (rs ranged from 0.03 to 0.39). Although most of these correlations suggest moderate informant agreement, there is also clear variation, so it is important to further study the sources of informant variation in degree of reported behavioral and emotional problems.[3]

9.2.2 Other Questionnaires and Item-Specific Analyses

In recent years, there has been an emerging interest in the possible co-occurrence of GD with autism spectrum disorders (ASD), as reviewed in de Vries, Noens, Cohen-Kettenis, van Berckelaer-Onnes, and Doreleijers (2010). A number of clinicians have reported on an apparent increase in the number of GD children and adolescents who appear to meet the criteria for a high-functioning ASD, such as Asperger's Pervasive Developmental Disorder Not Otherwise Specified. One explanation for a possible linkage between GD and ASD is the intense focus/obsessional interest in specific activities (e.g., Baron-Cohen & Wheelwright, 1999; Klin, Danovitch, Merz, & Volkmar, 2007). These children and adolescents appear to develop a fixation on gender, in much the same way that they develop other types of intense/obsessional/restricted interests (e.g., in street routes, in makes of dishwashers).

To address the idea of focused and obsessional interests, Wood et al. (2012) examined two items from the CBCL: Item 9 ("Can't get his/her mind off certain thoughts; obsessions") and Item 66 ("Repeats certain acts over and off; compulsions") in a sample of 534 GD children (439 boys, 95 girls) and 419 siblings (241 boys, 178 girls), who ranged in age from 3 to 12 years. As for all CBCL items, ratings were on a 0–2 point scale. The mother–father correlation was 0.50 for Item 9 and 0.39 for Item 66.

Item 9 was endorsed more frequently for the GD children than for the siblings (for males, 61.5 % vs. 27.3 %; for females, 66.7 % vs. 15.4 %), as was Item 66 (for males, 26.2 % vs. 10.5 %; for females, 21.5 % vs. 5.1 %). For Item 9, the percentage was even higher than for referred children in the standardization sample (for males, 49 %; for females, 47 %) and considerably higher than for non-referred children (for males, 24 %; for females, 20 %). For Item 66, the percentage was comparable to the referred children in the standardization sample (for males, 26 %; for females, 24 %) and considerably higher than for non-referred children (for males, 5 %; for females, 6 %).

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[3] There are several sources from which one can examine informant agreement on the CBCL, TRF, and YSR in the North American standardization samples (Achenbach, 1991, Tables 5–3, 5–4, 11–1, pp. 62, 64, 182; Achenbach & Edelbrock, 1983, Table 6–2, p. 45; Achenbach & Edelbrock, 1986, Table 4–3, p. 37; Achenbach & Edelbrock, 1987, Tables 7–1, 7–2, 7–3, pp. 108–109, 111). Across all of these comparisons, correlations for the three indices of behavioral problems (internalizing, externalizing, and total) ranged from 0.31 to 0.75.

Thematic analysis for Item 9 indicated that gender-related content was significantly more common for the GD boys than for their male siblings (54.6 % vs. 13.0 %), but the difference between GD girls and their female siblings was not significant (40.9 % vs. 26.3 %). For Item 66, gender-related content was not more prevalent among the GD children than among their siblings.

In a second study, Wood (2011) administered the Social Responsiveness Scale (SRS) (Constantino & Gruber, 2005) to the mothers of 38 GD children, seen either consecutively or at a routine follow-up. The SRS is a 65-item parent-report questionnaire, with response options ranging from 1 (not true) to 4 (almost always true). The SRS has five factors: Social Awareness, Social Cognition, Social Communication, Social Motivation, and Autistic Mannerisms. The last factor contains items that correspond to the construct of focused/intense interests (e.g., "Has an unusually narrow range of interests").

Wood (2011) found that 60.5 % of the sample had a T score ≥ 60 (indicating a clinical range score) on the Autistic Mannerisms factor. The corresponding percentages for the other factors were 39.5 %, 39.5 %, 47.4 %, and 44.7 %, respectively. For the total score, 55.3 % of the sample met criterion for caseness. Although these findings are suggestive of an elevation of ASD traits, much additional work is required; for example, it is not yet clear if these elevated traits of ASD in GD children will prove to be diagnostic specific—it is possible that they are characteristic of clinical populations in general (see, e.g., Pine, Guyer, Goldwin, Towbin, & Leibenluft, 2008).

9.2.3 Diagnostic Interview Schedules

Dimensional assessment of behavioral and emotional problems is, of course, not a formal equivalent to psychiatric categorical diagnoses; however, we are currently in an era where both methods of assessment are routinely used and are meant to complement one another (for a review, see Helzer et al., 2008). In this section, I review the studies that have relied on quasi-formal or formally structured diagnostic interview schedules that are based on DSM criteria for various psychiatric diagnoses.

Coates and Person (1985) used DSM-III criteria to assess separation anxiety disorder (SAD) in 25 boys (M age, 7.4 years) with GID via maternal report (the reason for the focus on SAD is discussed below). They reported that 60 % of the sample met criteria for SAD. Unfortunately, the interview procedure was not described and information on inter-rater reliability was not provided. Nonetheless, the high rate of SAD appears to converge with the CBCL behavior problem data reviewed above, which has suggested a predominance of internalizing behavior problems in GD boys (see, e.g., Zucker & Bradley, 1995).

In a subsequent study, Zucker, Bradley, and Lowry Sullivan (1996) transformed the DSM-III SAD criteria into a structured interview schedule consisting of 21 questions answered as "Yes," "Sometimes," or "No." It was administered to the mothers of 115 GID boys (M age, 6.3 years). Fifteen of the interviews were selected, at random, from the interviews that had been audiotaped ($n = 62$). Of the 315 questions, two coders had identical ratings for 302 (95.8 %). Cronbach's alpha for the interview schedule was 0.78.

Two methods of diagnosis were used. A "conservative" criterion for SAD required that the mothers answered "Yes" in three of the nine content domains, as was required in the DSM-III. A "liberal" criterion for SAD required that the mothers answered "Sometimes" or "Yes" in three of the nine content domains.

Zucker et al. (1996) compared the prevalence of SAD for the boys threshold and subthreshold for the diagnosis of GID. Using the conservative criterion, 17 (23.3 %) of the boys threshold for GID met criterion for SAD, compared to 4 (9.5 %) of the boys subthreshold for GID, a nonsignificant difference. Using the liberal criterion, 47 (64.4 %) of the boys threshold for GID met criterion for SAD, compared to 16 (38.1 %) of the boys subthreshold for GID, a significant difference.

Boys threshold for GID was significantly younger than the boys subthreshold for GID; in addition, boys who met the liberal criterion for SAD were more likely to come from a mother-only or "reconstituted" family than the boys who did not. In a logistic regression analysis, parent's marital status and the diagnosis of GID increased the odds of a liberal diagnosis of SAD by factors of 6.3 and 3.7, respectively. Age was not a significant predictor. In a second logistic regression, the presence of a SAD diagnosis increased the odds of a GID diagnosis by a factor of 4, and age decreased the odds of a GID diagnosis by a factor of 0.5 (for each year of age). Parent's marital status was not a significant predictor.

Wallien, Swaab, and Cohen-Kettenis (2007) administered the Diagnostic Interview Schedule for Children-Parent version (DISC-P) to the parents of 120 GD children (86 boys, 34 girls) ages 4–11 years and to the parents of 47 children (37 boys, 10 girls) referred to an ADHD clinic at the same hospital. Analyses focused on the modules that pertained to internalizing (anxiety and mood disorders) and externalizing (disruptive behavior disorders) problems.

Wallien et al. (2007) reported that 52 % of the GD children met criteria for at least one DISC-P diagnosis. In the entire sample, 23 % met criteria for one diagnosis and 29 % met criteria for two or more diagnoses. These percentages were comparable to that of the ADHD group: 59 % met criteria for at least one DISC-P diagnosis other than ADHD. In the entire sample, 23 % met criteria for one diagnosis and 36 % met criteria for two or more diagnoses.

de Vries, Steensma, Doreleijers, and Cohen-Kettenis (2012) administered the Diagnostic Interview Schedule for Children-Parent version (DISC-P) to the parents of 105 GD adolescents (53 males, 52 females) ages 10–18 years (M age, 14.6 years). de Vries et al. reported that 32 % of the GD adolescents met criteria for at least one DISC-P diagnosis. In the entire sample, 18 % met criteria for one diagnosis and 14 % met criteria for two or more diagnoses.

de Vries et al. (2010) administered the Dutch version of the Diagnostic Interview for Social and Communication Disorders (DISCO-10), which assesses autism spectrum disorders (ASD), drawn from a sample of 204 GD children and adolescents (115 boys, 89 girls), with a mean age of 10.8 years. The DISCO-10 was administered to the mothers of a selected number of patients from whom an ASD was suspected. The prevalence of an ASD was 7.8 %. de Vries et al. noted that the percentage was lower among patients threshold for GID (4.7 %) compared to the patients with a diagnosis of GID Not Otherwise Specified (17.0 %). de Vries et al. noted that the 7.8 % prevalence was 10 times higher than the prevalence of 0.6–1 % of ASD in the general population.

9.2.4 Projective Testing

There is a small literature using projective testing with children and adolescents with GD, primarily with the Rorschach test. On different scales that measure psychopathology on the Rorschach (e.g., with regard to indices of object relations and thought disturbance), boys with GID have, on average, shown more impairment than non-referred controls (Goddard & Tuber, 1989; Ipp, 1986; Kolers, 1986; Tuber & Coates, 1989; see also Tuber & Coates, 1985). However, Ipp (1986) and Kolers (1986) found that the siblings of the GID boys were equally impaired, and Goddard and Tuber (1989) found that GID boys with a diagnosis of SAD were, by and large, no more impaired than clinic-referred boys with SAD. Cohen, de Ruiter, Ringelberg, and Cohen-Kettenis (1997) reported that GD adolescents (9 males, 29 females) were intermediate between that of 24 other clinic-referred adolescents (8 males, 16 females) who had been administered the Rorschach and 25 non-referred female controls on a measure of perceptual inaccuracy, but not with regard to a measure of thought disturbance or negative self-image. The wide range of dependent measures and less than optimal sampling strategies call for caution in interpreting these findings. If anything, it is likely that children with GD do not have particularly unique Rorschach protocols, but they may well share signs of impairment characteristic of clinical samples in general. In this respect, the data may parallel the findings of behavior problems detected on better-validated measures, such as the CBCL and YSR.

9.3 Models of Psychopathology

9.3.1 Psychodynamic Formulations

In the early literature on psychopathology in children with GD, which was advanced primarily by Stoller's (1968a, 1968b) work on GD boys, it was argued that these boys did not show any particular type of psychopathology. In fact, Stoller argued that, apart from their extreme GD, these boys were virtually "normal." His theoretical model focused more on why they had developed extreme GD in its own right. The model was a systemic one: Complex family dynamics and psychopathology, perhaps building on certain predispositions in the boys (e.g., their physical "beauty"), produced the GD. The GD was ego-syntonic for the boys because the family dynamics that had produced it were systemically syntonic.

In a subsequent model, Coates and Person (1985) took a very different position. Coates and Person provided data showing that GD boys had high rates of co-occurring psychopathology (as measured via maternal report—see Table 9.1), with a particular emphasis on separation anxiety (as noted above). In this model, GD was conceptualized as secondary to the underlying psychopathology of separation anxiety:

> *"…to restore a fantasy tie to the physically or emotionally absent mother…[in] imitating 'Mommy' [the boy] confuse[s] 'being Mommy' with 'having Mommy.' [Cross-gender behavior] appears to allay, in part, the anxiety generated by the loss of the mother"* (p. 708).

It is of interest to note that these two psychodynamically informed models of psychopathology led to two rather diametrically opposite conclusions. Although both models were concordant in hypothesizing complex family dynamics leading to the development of GD, they reached very different conclusions regarding the presence of associated psychopathology: In Stoller's model there was none; in Coates and Person's model, it was pervasive.

9.3.2 Social Ostracism

This model argues that the presence of associated psychopathology in children and adolescents with GD is secondary to the experience of social ostracism (e.g., within the peer group). It is well established that marked gender-variant behavior (the surface expression, at least in some cases, of the underlying GD) is reacted to negatively in the social environment and it is this social reaction that produces the other forms of psychopathology. Because the normative literature shows that gender-variant behavior is reacted to more negatively in boys than in girls within the peer group (e.g., Blakemore, 2003; Fagot, 1977; Zucker, Wilson-Smith, Kurita, & Stern, 1995), one could argue that poor peer relations, especially with same-sex peers, will be more impaired in GD boys than in GD girls. In a broader context, this model can be conceptualized as an element of the minority stress that can be experienced by any gender nonconforming person across the life-span (see, e.g., Baams, Beek, Hille, Zevenbergen, & Bos, in press; Harry, 1983; Meyer, 2003; Rieger & Savin-Williams, 2012).

Green (1976) had mothers of feminine boys and masculine control boys classify their peer relations with other boys into one of the four categories: "leader," "good mixer," "voluntary loner," or "rejected."[4] Figure 9.1 shows these data. It can be seen that the masculine boys were much more likely to be classified as good mixers in a male peer

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[4] Green's study was conducted prior to the introduction of the GID diagnosis for children in DSM-III. Many of the boys in his study would probably have met the criteria for GID.

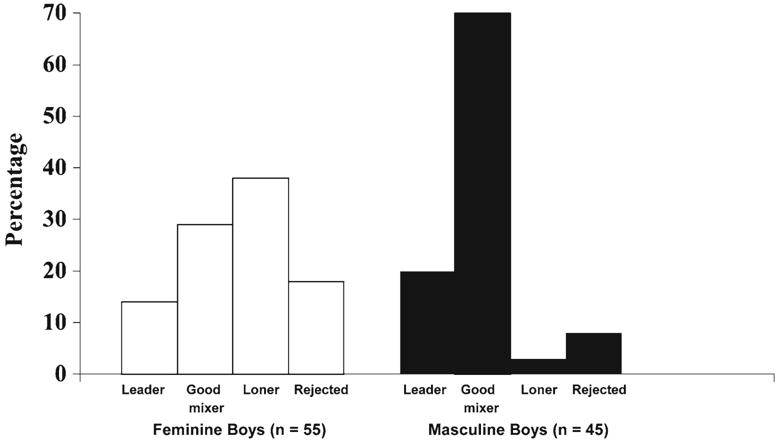


Fig. 9.1 Maternal ratings of same-sex peer relations in feminine and masculine boys [data from Green (1976)]

group than were the feminine boys, whereas the feminine boys were more likely to be classified as either loners or rejected than were the masculine boys. In a further analysis of these data, Zucker et al. (1995) reported that the feminine boys classified as rejected were significantly older (M age, 8.8 years) than were the boys classified in the other three categories (M ages, 6.6, 6.8, and 5.8 years, respectively). Thus, overt rejection appears to occur starting around Grade 3 in North American schools.

In a subsequent study of ad-recruited "tomboys" and "non-tomboys," Green, Williams, and Goodman (1982) had the mothers provide the same classification for peer relations with other girls. Figure 9.2 shows these data. It can be seen that the non-tomboys were more likely to be classified as good mixers in a female peer group than were the tomboys, and the tomboys were more likely to be classified as loners than were the non-tomboys. However, unlike the data for feminine boys, rejection of tomboys by female peers did not occur.

Wallien, Veenstra, Kreukels, and Cohen-Kettenis (2010) examined the social position of 28 GD children (14 boys, 14 girls) in the naturalistic environment. Each child and his or her classmates (M, 19.4 children/class) participated in a sociometric peer nomination procedure. For various measures, the children could nominate as many of their classmates as they desired.

Figures 9.3–9.6 show proportion scores (which could range from 0 to 1) of nominations for acceptance and rejection for GD children and their same-sex classmates. In Fig. 9.3, it can be seen that GD boys were less likely to be accepted than were the other boys in the class by their same-sex peers and somewhat more likely to be rejected. In contrast, it can be seen in Fig. 9.4 that GD boys were more likely to be accepted than were the other boys in the class by the girls and less likely to be rejected. In Fig. 9.5, it can be seen that GD girls were less likely to be accepted than were the other girls in the class by their same-sex peers, but were no more or less

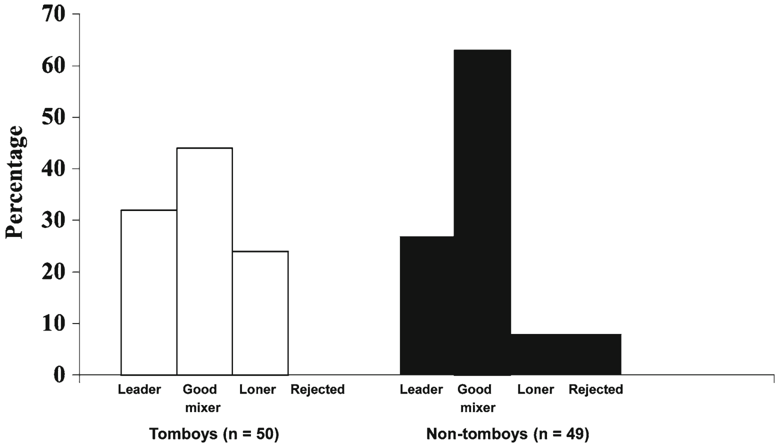
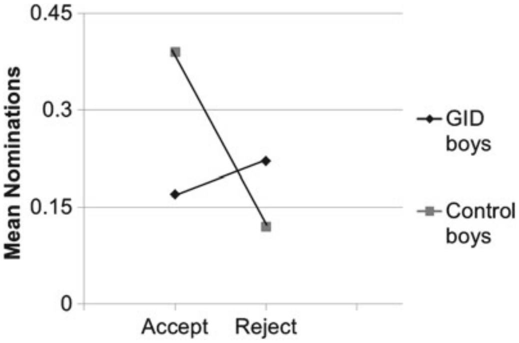


Fig. 9.2 Maternal ratings of same-sex peer relations in tomboys and non-tomboy girls [data from Green et al. (1982)]

Fig. 9.3 Peer acceptance and rejection by boy classmates of gender-dysphoric boys [data from Wallien et al. (2010)]



likely to be rejected. In Fig. 9.6, it can be seen that the GD girls were more likely to be accepted than the other girls in their class by the boys and less likely to be rejected than the other girls. Thus, in this study, there was more cross-sex acceptance of both GD boys and girls, but only the GD boys were more rejected by same-sex peers when compared to other children of the same sex. It appears, therefore, that the experience of rejection by same-sex peers is more salient for GD boys than it is for GD girls. It is also very clear from this study that the peer relations of GD children and that of control children are strongly related to the sex of the peer group.

An experimental study by Fridell (2001) provided further evidence that the cross-sex-typed behavior of GD boys may well be related to how well they are liked by other children. Fridell created 15 age-matched play groups consisting of one boy with GD and two non-referred boys and two non-referred girls (age range, 3–8 years). After two 60-min play sessions, conducted a week apart, each child was asked to select their favorite playmate from the group. The non-referred boys chose most often the other non-referred boy as their favorite playmate, thus indicating a

Fig. 9.4 Peer acceptance and rejection by girl classmates of gender-dysphoric boys [data from Wallien et al. (2010)]

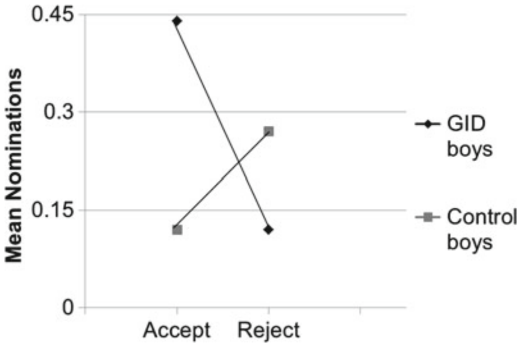


Fig. 9.5 Peer acceptance and rejection by girl classmates of gender-dysphoric girls [data from Wallien et al. (2010)]

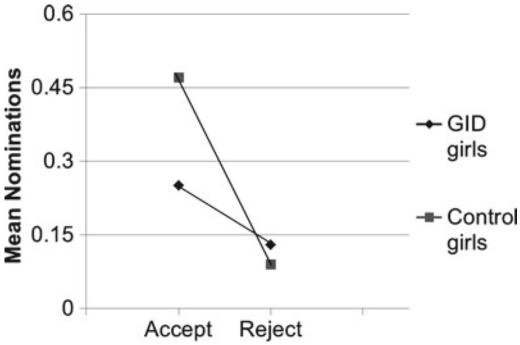
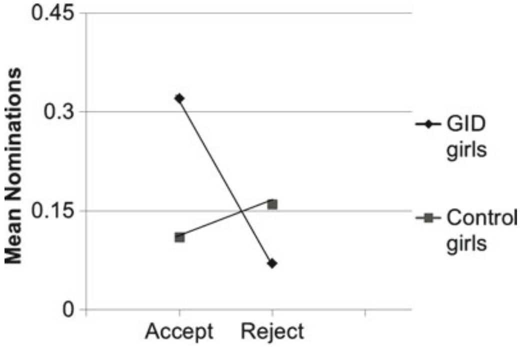


Fig. 9.6 Peer acceptance and rejection by boy classmates of gender-dysphoric girls [data from Wallien et al. (2010)]



distinct preference over the boy with GD. The non-referred girls chose the other girl as their favorite playmate, thus showing a relative disinterest in either the boy with GD or the two non-referred boys.

Zucker, Bradley, and Sanikhani (1997) constructed from the CBCL a (poor) Peer Relations Scale, which consisted of three items: “Doesn’t get along with other kids” (Item 25), “Gets teased a lot” (Item 38), and “Not liked by other kids” (Item 48). Data were obtained for both children with GID and their siblings. Cronbach’s alpha was 0.81. In the Zucker et al. (2012) study of GD adolescents, Cronbach’s alpha was 0.82 for this scale. On the YSR, the corresponding alpha was 0.63 and, on the TRF (Steensma et al., 2012), the corresponding alpha was 0.82.

Compared to their siblings, Zucker et al. (1997) found that GD children had significantly poorer peer relations, even with the total number of other endorsed CBCL problems covaried. In Cohen-Kettenis et al. (2003), Steensma et al. (2012), and Zucker et al. (2012), GD males had significantly poorer peer relations than GD females. This sex difference was remarkably consistent: It was reported by mothers, by teachers, and by self-reports and it was detected in both children and adolescents.

Although the sex difference in poor peer relations was similar across informants in the Amsterdam and Toronto clinics, there was also evidence of a cross-clinic, cross-national difference in the degree of poor peer relations, at least to some extent. On the one hand, there was no significant cross-clinic difference in mother-rated poor peer relations for GD children. On the other hand, on the TRF, both children and adolescents in the Toronto clinic had poorer peer relations than did the children and adolescents in the Amsterdam clinic (Steensma et al., 2012), and a similar pattern was found for both CBCL and YSR ratings of the adolescents (de Vries et al., unpublished data). Steensma et al. (2012) plotted the TRF ratings for poor peer relations as a function of age. Although the Toronto children had somewhat poorer peer relations than the Dutch children 8 years of age or younger, the difference increased sharply at the age of 9–10 years and remained substantially higher through the age of 18 years. This cross-national difference was interpreted as a reflection of greater tolerance (or at least inhibition of marked rejection) in Dutch culture than in Canadian culture.

Regression analysis of the CBCL data and the TRF data showed that poor peer relations were a very strong predictor of general behavior problems. For children in Cohen-Kettenis et al. (2003), R^2 was 0.34 for prediction of CBCL behavior problems, and in Steensma et al. (2012), R^2 was 0.48 for prediction of TRF behavior problems in boys and 0.35 for behavior problems in girls.

In an earlier study, Zucker (1990) showed that being called a "sissy" (on a 1–5 point response scale) was the strongest predictor of CBCL psychopathology across six indices in a sample of 77 GD boys (βs ranged from 0.31 to 0.41, all $p\text{s} < 0.01$).

In summary, it appears that social ostracism is an important correlate of general behavior problems in children and adolescents with GD. One could, however, argue that the direction of effect is the other way round, i.e., the general behavior problems of GD children and adolescents lead to social ostracism. However, the principle of parsimony would suggest that it is the gender-variant surface behavior of GD children and adolescents that plays the central causal role. This could be tested by assessing behavior problems in GD children and adolescents as a function of social environments that vary in the degree of peer acceptance of gender-variant behavior.

9.3.3 General Risk Factors

Another model argues that the presence of associated psychopathology in children and adolescents with GD is related to generic risk factors. That is, the presence of

Table 9.2 Predictors of behavior problems in boys with GD

Behavior problem informant	Significant predictor variables
Mother	Step 1: Peer Relations Scale ($R^2 = 0.370$) Step 2: Maternal psychopathology ($R^2\mathrm{D} = 0.133$) Step 3: Full-Scale IQ ($R^2\mathrm{D} = 0.019$)
Father	Step 1: Peer Relations Scale ($R^2 = 0.284$) Step 2: Full-Scale IQ ($R^2\mathrm{D} = 0.043$) Step 3: Age ($R^2\mathrm{D} = 0.021$) Step 3: Maternal psychopathology ($R^2\mathrm{D} = 0.016$)
Teacher	Step 1: Peer Relations Scale ($R^2 = 0.217$) Step 2: Full-Scale IQ ($R^2\mathrm{D} = 0.042$) Step 3: Maternal psychopathology ($R^2\mathrm{D} = 0.024$) Step 4: Child's cross-gender behavior ($R^2\mathrm{D} = 0.021$)

Note. The nine predictor variables were the child's age at assessment, Full-Scale IQ, parent's social class and marital status, the CBCL poor peer relations composite, the Gender Identity Questionnaire for Children, a composite measure of maternal psychopathology, a measure of marital/relational adjustment, and the mother's recall of her own sex-typed behavior during childhood. The criterion variable was the sum of behavior problems on the CBCL or TRF rated as a 1or a 2 (with the three items comprising the Peer Relations Scale removed). All predictors were significant at $p < 0.05$

"general" psychopathology in children and adolescents with GD is related to risk factors that would be associated with psychopathology in any child or youth (e.g., a family history of psychiatric disorder, concurrent parental psychopathology and relational discord, social class background) (e.g., Connell & Goodman, 2002). In this model, the presence of associated psychopathology is not deemed as related to the development of GD per se.

There is some evidence that supports the role of general risk factors in accounting for some of the variance in behavior problems for GD children. Zucker (2005b, 2008) reported on a data set that contained a sample of 245 GD boys (M age, 6.9 years). Measures included demographic variables, a parent-report measure of their son's sex-typed behavior, measures of maternal psychopathology (e.g., on the Symptom Checklist-90-Revised, the Diagnostic Interview Schedule), and a measure of marital/relational adjustment.

In this study, a multiple regression analysis included nine predictor variables and the criterion variable was the sum of items rated as a 1 or a 2 on the CBCL. Table 9.2 shows the results of this analysis: It indicated that there were three significant predictors of CBCL behavior problems: the Peer Relations Scale from the CBCL (described above), a composite measure of maternal psychopathology, and the child's Full-Scale IQ (with lower scores related to more CBCL behavior problems).

Given that the mothers were the informants for the CBCL data and their own psychopathology, this raises the potential for bias: Do mothers with more psychopathology have "distortions" in ratings of their child's behavior problems, i.e., do they "overreport" (see, e.g., Richters, 1992)? To address this question, paternal report of CBCL was used as the criterion variable in a second regression analysis. As shown in Table 9.2, maternal psychopathology was a significant predictor of paternal report of CBCL behavior problems. Table 9.2 also shows that maternal psychopathology was also a significant predictor of behavior problems reported by teachers on the TRF. Thus, this data set appears to support the hypothesis that behavior problems in children with GD can, at least in part, be accounted for by general measures of maternal psychopathology.

9.3.4 Gender Dysphoria as an Inherent Cause of Distress and Psychopathology

A remarkably understudied question is to the extent to which gender dysphoria per se causes "inherent" distress, which, in turn, produces other types of psychopathology (e.g., depression, substance abuse). Although Stoller (1985) characterized GID in young boys as a type of "developmental arrest" (p. 38), he did not detect much in the way of inherent distress or psychopathology:

> *"…marked femininity in anatomically and genetically normal boys can begin in an ambience of excessive gratification and too little conflict, trauma, and frustration"* (p. 38).

As noted earlier, his model contrasts sharply with the formulation by Coates and Person (1985), in which the marked cross-gender identification was conceptualized as a defensive maneuver to protect against marked separation anxiety and other sources of severe stress (Coates, 1985, 1990; Coates, Friedman, & Wolfe, 1991). The social ostracism model implies that much of the associated psychopathology would disappear if the social environment was more supportive. In our view, there has been very little research that has attempted to evaluate distress as a direct function of GD in both children and adolescents. In some respects, this is surprising because the DSM diagnostic criteria require that the clinician ascertain the presence of distress as part of the distress/impairment criterion. Consider the following pieces of clinical data:

1. Mother of a 3-year-old natal male: My son…says that he is a girl. I tell him he was born a boy (Interviewer: What does he say to that?). He has a temper tantrum, crying, and he rolls around on the floor for 45 min, saying that he is a girl.
2. Mother of a 4-year-old natal male: My son is happy as long as he is dressed in girls' clothes. When asked to take them off for bedtime, he cries.
3. Mother of a 6-year-old natal male: He's the happiest kid in the world…except one thing. He wants to be a girl and cut off his penis.
4. Mother of a 6-year-old natal female: My daughter begs her father to transfuse his genes into her.
5. Mother of an 8-year-old natal female: My daughter wants to die and be reborn as a boy [the family is Buddhist].
6. A 17-year-old natal male: When I look in the mirror, the person isn't me…the male features I see make me depressed, appalled. I don't have confidence in myself as a male. When I cross-dress, I feel more confident…I don't like my penis…I ignore it…Certain girls make me feel depressed because I envy them… that I will never be pregnant or look like them.

7. An 18-year-old natal female: My parents have accepted me as “trans.” My friends support me. My breasts are like tumors. I want to tear them off. If you don’t approve me for sex-reassignment surgery, I am going to kill myself.

Suppose one had measures of “support” within the social environment for a child’s or adolescent’s strong desire to be of the other gender. Support could be gauged via measures of parents’ reactions to their child’s cross-gender behavior and within the peer social network. In a strongly supportive psychosocial milieu, would there be much in the way of “other” psychopathology in GD children and adolescents? To what extent do children and adolescents report distress about their gender-dysphoric feelings, and, if such distress is present, does it correlate with general measures of psychopathology? In our view, there are little data available to answer these questions in Western samples of GD children and adolescents.

It is now well recognized that there are non-Western cultures that have “third-gender” categories of individuals who do not “fit” into the gender binary of male vs. female (Herdt, 1994). To some extent, these third-gender individuals share a phenomenology or subjectivity that has a lot in common with GD individuals from Western culture. In Samoa, the third-gender category of the *fa’afafine* is a prototype example. The *fa’afafine* are genetic males who transition to a third-gender category at some point in the life course. In childhood, their sex-typed behavior is female typical (Bartlett & Vasey, 2006), and, in adulthood, they are sexually attracted to heterosexual males. The *fa’afafine* are generally accepted in Samoan culture although their social status is not entirely stigma-free (Vasey & Bartlett, 2007). Interestingly, Vasey, VanderLaan, Gothreau, and Bartlett (2011) reported that *fa’afafine* adults recalled more separation anxiety in childhood than heterosexual men and heterosexual women, a finding that converges with Western data on traits of separation anxiety in GD boys. Vasey and Bartlett argued that only a minority of *fa’afafine* appear to experience distress regarding the incongruence between their felt gender identity and somatic sex and that most did not recall experiencing distress about their cross-gender identity during childhood.

Perhaps the lack of distress reflects a combination of within-family support of the childhood signs of a *fa’afafine* identity in statu nascendi and a more generally supportive cultural milieu. At the same time, one wonders if the transition to a *fa’afafine* third-gender status is fuelled by the individual’s recognition that “he” is not a gender-typical male, which causes a sense of personal distress and leads to the gender transition. On this point, it is our view that more ethnographic fieldwork is required.

9.4 Summary and Conclusions

Understanding the empirical evidence that supports or contests these different models is extremely important with regard to clinical management policies and decisions. If Stoller’s model is correct and the therapeutic aim is to reduce the GD by psychotherapeutic methods, then the treatment would attempt to address the underlying systemic psychopathology and dynamics that purportedly produced the GD.

If Coates and Person's model is correct, and the therapeutic aim is to reduce the GD by psychotherapeutic methods, then the focus of treatment would be to address the underlying separation anxiety hypothesized to produce the GD as a kind of "fantasy solution" or "compromise formation" (Coates et al., 1991) that functions to alleviate the primary pathology (i.e., the separation anxiety). If the model of social ostracism is correct, one therapeutic approach would be to reduce the child's expression of gender-variant behavior. If these children became more gender typical, it would eliminate the surface behaviors that elicit the social ostracism. An alternative therapeutic approach would be to provide the child a safer social environment (e.g., attendance at schools in which gender nonconforming behavior is better tolerated, if not embraced, or to work with parents around "accepting" their child's gender-variant behavior) (see, e.g., Ehrensaft, 2011a, 2011b; Hill & Menvielle, 2009; Menvielle, 2009, 2012; Menvielle & Hill, 2011; Riley, Sitharthan, Clemson, & Diamond, 2011; Wilson, Griffin, & Wren, 2005). If the model of generic risk factors is correct, then the focus of treatment would be to alleviate, where possible, the activating effects of such factors (e.g., reduction of concurrent parental psychopathology, pharmacological treatment of the child when they have disorders that might be related to an underlying biological diathesis). If the association with an ASD is correct, then one therapeutic approach would be to help a child think more flexibly regarding gender, to move the child away from the intense/restricted focus on gender, etc. Finally, if GD is an inherent source of distress, then treatment designed to eliminate the GD (whether by psychotherapeutic methods or biomedical treatments) should reduce the associated psychopathology. There is certainly some evidence in GD adolescents that biomedical treatments are related to a reduction in psychopathology (Cohen-Kettenis & van Goozen, 1997; de Vries, Steensma et al., 2012; Smith, van Goozen, & Cohen-Kettenis, 2001). For GD children, however, we still know very little regarding the effects of psychotherapeutic methods that attempt to reduce the GD in children and associated psychopathology when it is present or about the effects of supportive, affirmative approaches to GD and their concomitant impact on associated psychopathology.

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Chapter 10
Early Medical Intervention in Adolescents with Gender Dysphoria

Henriette A. Delemarre-van de Waal

Abstract During the last 10 years, the Dutch protocol that comprises medical intervention in the management of gender dysphoria in adolescents has appeared to be safe and efficient. Using GnRH analogs, physiologic pubertal development is suppressed. From the age of 16 years, cross-sex steroids are added to the GnRH analog to induce the pubertal sex characteristics of the desired sex.

Side effects of the GnRH analog treatment are conceivable in the areas of growth, bone development, metabolism, and brain development. Up until now, however, we have not observed major side effects. On the contrary, with respect to growth, when medical intervention is started early in puberty, we are able to manipulate growth in a way that final adult height is more appropriate for the desired sex.

Currently, before the treatment is started to suppress puberty (with GnRH analogs) or to induce puberty (with cross-sex hormones), the treatment guidelines suggest to medical professionals that adolescents should have reached a certain pubertal stage, as well as a certain age. Because of the current positive outcomes, protocols may permit an earlier start to puberty suppression and induction of cross-sex secondary sex characteristics. This would result in a more typically timed physiologic pubertal development in adolescents with gender dysphoria.

10.1 Introduction

In the 1970s, treatment of gender identity disorders (GID) started with an experimental design in adults (Asscheman, Gooren, & Eklund, 1989). Female-to-male transsexuals (FtMs) were treated with androgens, while male-to-female

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transsexuals (MtFs) received cyproterone acetate to suppress androgen activity, combined with estrogens. The morbidity and mortality of this relatively young population was higher compared to a reference population (Asscheman et al., 1989). Over time, the management in adults has been improved and adjusted for individual patients (Gooren, 2011).

The supportive care for prepubertal children with GID is predominantly psychological. Since the late 1990s, the possibility of puberty suppression when GID persists during adolescence has generated a new but still controversial dimension to clinical management. Puberty suppression is considered a fully reversible medical intervention that can serve as a diagnostic aid in gender dysphoric adolescents. It provides the gender dysphoric adolescent with time and rest before a more definite decision is made on (partially) irreversible steps of gender reassignment (cross-sex hormones and surgeries). However, this early treatment of adolescents revealed concerns about potential risks, such as a poor physical and psychological outcome due to adverse effects of puberty suppression on bone and brain development, respectively. An important concern is whether an adolescent is capable of making such a major decision. The first gender dysphoric adolescents for whom puberty was suppressed were far in their pubertal development when treatment was applied using gonadotropin-releasing hormone (GnRH) analogs.

Case History

The first patient Peggy Cohen-Kettenis and myself treated was a 13-year-old girl in pubertal Tanner stage four (Cohen-Kettenis et al., 2011). Treatment consisted of a GnRH analog, followed by a combination with androgens. At the age of 20 and 22 years, she underwent reassignment surgery, and thereafter medication consisted of only androgens. During the follow-up at 22 years of age, he indicated he had no regrets about this treatment. He was functioning well psychologically, intellectually, and socially. There were no clinical signs of physical imbalance; metabolic and endocrine (male) parameters were in the normal reference range, as was bone density. He believed himself in good physical health.

This long-term follow-up of puberty suppression suggested that such a treatment can be a useful tool in the diagnosis and treatment of gender dysphoric adolescents.

A treatment protocol based on both aspects (diagnostics and treatment) was composed, which was included in the official guidelines of the American Endocrine Society and the European Society of Pediatric Endocrinology (Delemarre-Van de Waal & Cohen-Kettenis, 2006; Hembree et al., 2009).

Although this approach is increasingly accepted, the treatment of adolescents with GID is still under debate among professionals and policy makers. Therefore, we still need to collect data on the health outcome of adolescents treated for gender dysphoria.

10.2 Ethical Aspects of Clinical Management: Why Should We Treat Adolescents with Gender Dysphoria?

There are still many questions about whether or not the treatment of adolescents with GID is ethical. Aren't these youngsters too young to be fully cognizant of the consequences of their choices? Although the use of puberty suppressants is described in international guidelines, there is no worldwide consensus on the Endocrine Society Guidelines and the Standards of Care of the World Professional Association of Transgender Health (Coleman et al., 2012; Hembree et al., 2009). In the Netherlands, puberty suppression is part of the treatment protocol for gender dysphoric adolescents. In recent years, various countries in North America and Europe have adopted this model of care that is sometimes referred to by the country of its developers: "The Dutch approach" (Olson, Forbes, & Belzer, 2011; Spack et al., 2012; Zucker, 2010). However, in some countries, it is not the standard of care due to various ethical concerns, including fears about harm from the treatment. Concerns that are raised include the following: Can a reliable diagnosis of GID be made in children and adolescents? Is there psychopathology involved in the child with GID and his or her parents that obscures this diagnosis?

Suppression of puberty resulting in "freezing" puberty may help in the diagnostic phase by "buying time." In collaboration with both a medical and mental health professional, the adolescents may explore their gender identity without the distress of developing secondary sex characteristics. If the adolescents want to live permanently in the desired gender role as adults, they will be spared the torment of the "wrong" secondary sex characteristics.

With regard to side effects of the treatment, suppression of puberty will have its influence on height, bone development, and possibly on metabolism (for carbohydrates and lipids). The question is whether these side effects are always harmful; with respect to height, an early intervention in a male-to-female transsexual may result in a more acceptable "female" final height. Other aspects of debate are the loss of fertility in males in case of early treatment, as well as the influence on gender identity development and brain development. Finally, one may have concerns regarding the costs of treatment associated with GID. Before discussing these aspects, a more detailed description of the Dutch protocol will be given.

10.3 Treatment Protocol: The Dutch Experience

For prepubertal children, treatment includes psychological counseling. When GID persists into adolescence, suppression of puberty can be considered.

The first adolescents for whom puberty was suppressed were treated with progestins and modified sex steroids (cyproterone acetate). These drugs exert a negative feedback on the secretion of gonadotropins, resulting in lower gonadotropin and sex steroid levels. In addition, most of these drugs have a direct negative effect on the activity of sex steroids as a blocker at the steroid receptor level. This suppression was often incomplete, resulting in a slow continued progression of pubertal development including skeletal maturation, although height velocity decreased (Lee, Thompson, Migeon, & Blizzard, 1975).

The availability of GnRH analogs in the 1980s gave the opportunity to suppress the gonadotropins more adequately. These analogs have prolonged binding at the GnRH receptor, resulting in desensitization and a complete block of gonadotropin release. A complete block of the endocrine and clinical pubertal development occurs. The GnRH analogs were originally developed in order to suppress gonadotropin secretion in central precocious puberty (Boepple et al., 1986). Thirty years of experience since its introduction revealed that this treatment is safe and, most importantly, very effective at suppressing puberty. Discontinuation of the analog showed a rapid recovery of the gonadotropin axis and, in girls, restoration of the menstrual cycle. At the moment, the main official indication to use GnRH analogs in children is central precocious puberty (Carel et al., 2009).

Because of its efficacy to suppress gonadotropin secretion, GnRH analogs are the optimal treatment option in the management of a pubertal girl or boy with GID. The first GID patients we treated were in the second half of puberty, and consequently the girls may have experienced menarche and boys may have already shown signs of masculinization, such as lowering of the voice. The GnRH analogs completely suppress gonadotropin and sex steroid levels; estradiol levels in girls are not detectable anymore, and testosterone levels in boys are below 1.0 nmol/L. Clinically, in girls, breast mass will become weak and diminish. A problem in boys is that masculinization, such as outgrowth of the cheeks and lowering of the voice, is not reversible. That means that although testicular volume decreased, the visible sex characteristics as result of androgen exposure remained.

Seeking the best way of treating children with GID, we started the GnRH analog in adolescents with some early pubertal development. For girls, this means that they are in Tanner stages 2–3, with budding of the nipple or slightly more volume of the breast and measurable estradiol levels. For boys, Tanner stage 3 is characterized by testicular volume of about 10 ml and measurable testosterone levels. The start of puberty is considered of diagnostic value, since most adolescents experience an aggravation of their distress resulting from gender dysphoria. They may not want to be confronted with their bodies, may not take showers anymore, and may refuse physical examinations.

GnRH analogs immediately halt pubertal progression. In addition to the effects on the sex characteristics, skeletal age is delayed and height growth continues in a prepubertal velocity (Delemarre-Van de Waal & Cohen-Kettenis, 2006). Follow-up measurements of the endocrine parameters revealed an adequate suppression of gonadotropins, while other endocrine systems remained in the normal range. Therefore, GnRH analogs appear to be an effective and safe treatment in order to stop endogenous pubertal development. An advantage of this intervention is that it is fully reversible; discontinuation will restore endogenous pubertal development.

Table 10.1 Treatment schedules to initiate pubertal development

Induction of female puberty with 17-beta estradiol, increasing the dose every 6 months
5 μg/kg/day
10 μg/kg/day
15 μg/kg/day
20 μg/kg/day
Adult dose = 2 mg per day
Induction of male puberty with testosterone esters increasing the dose every 6 months
25 mg/m^2/2 weeks im
50 mg/m^2/2 weeks im
75 mg/m^2/2 weeks im
100 mg/m^2/2 weeks im
Adult dose 250 mg per 3–4 weeks

The next step of treatment is to start cross-sex hormones. This treatment is partially reversible, meaning that the achieved changes in external sex characteristics will not disappear completely after discontinuation of the sex steroids. The age we start with cross-sex hormones is 16 years and is based on the fact that in the Netherlands (as in many European countries), a 16-year-old is a legal adult for medical decision making. Parental consent is not obligatory but is preferred, since the adolescent needs social support in this complex phase of life.

In the first step of treatment with GnRH analogs, we make the patient hypogonadotropic without gonadal sex steroids. To induce female sex characteristics in MtFs, estrogens are prescribed in an increasing dose as shown in Table 10.1. Breast development and female-appearing body shape will be initiated. When patients are on an adult dose, this will be continued for the rest their lives. Once a patient is older than 16 years of age, the levels of the dose can be adjusted. In FtMs, androgens induce virilization, including male body features such as a low voice, facial and body hair growth, and a more masculine body shape. Androgen treatment will also result in clitoral enlargement, although the final size will never reach the size of a normal penis. If still present, mild breast mass will become more atrophic and may even disappear. Also, in FtMs older than 16 years of age, the treatment schedule can be sped up.

10.4 Physical Aspects of Treatment of Adolescents with Gender Dysphoria

10.4.1 Growth

Suppression of puberty will delay height velocity and skeletal maturation. It appears that a delay in growth will remain and will result in catch-up growth at a later phase. The patient will continue to grow with prepubertal height velocity. The problem for

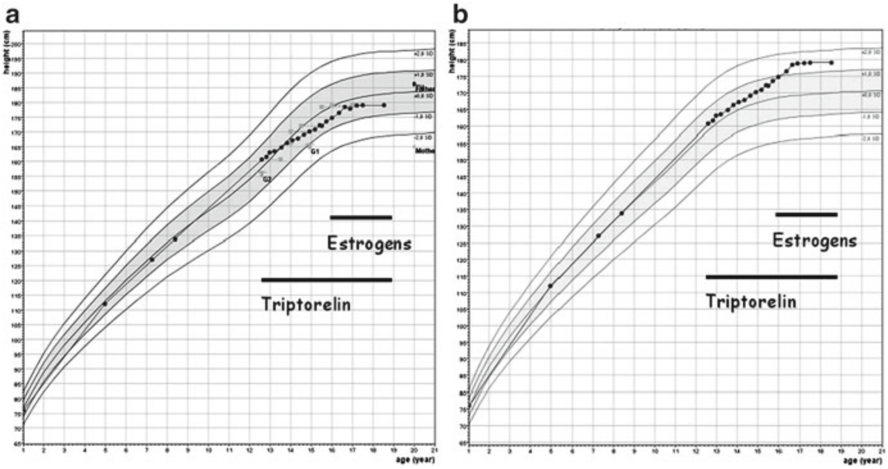

Fig. 10.1 Growth curve, depicted on a male (**a**) and female curve (**b**), respectively, of a MtF transsexual during treatment with GnRH analog and during combination treatment of GnRH analog (Triptorelin^R) with estrogens from the age of 16 years. Patient was in Tanner stage G2 at start of the treatment. Since testicular volume decreased to below 4 ml, pubertal stage regressed to G1. [This figure is reprinted from Delemarre-Van de Waal and Cohen-Kettenis (2006)]

MtFs is that their adult predicted height is relatively tall for females. The mean adult difference in height between males and females is 12 cm in the Dutch population. Therefore, the MtF will want to limit the final height. The experience in MtFs is that, after several years of suppression of puberty, the growth curve crosses the SD (standard deviation) curves downwards (see Fig. 10.1) (Delemarre-Van de Waal & Cohen-Kettenis, 2006). When estrogens are started, a small catch-up can be seen, followed by a decrease in height velocity. If (female) tall stature is expected, one can increase the estrogen dose in order to reduce final height.

The opposite is the case in FtMs, as Dutch females are on average 12 cm shorter than males. Suppression of puberty will stop the female pubertal growth spurt and a prepubertal height velocity will decrease height SD. Since female puberty on average starts 2 years earlier than male puberty, the FtMs need to be treated longer before androgens can be started at the age of 16 years. To increase height velocity, anabolic steroids can be used such as oxandrolone with a strong height velocity-stimulating effect and with a mild progressive effect on skeletal age. Our data show an increase in FtM's final height compared to predicted height when started with suppression of puberty.

In conclusion, medical intervention in gender dysphoric adolescents will influence height. However, this may be positive as MtFs may have a more appropriate female height and FtMs a more appropriate male height.

10.4.2 Bone Development

From the experience with suppression of puberty in girls with central precocious puberty (CPP), we know that bone mass can be lost. At start of treatment, girls with CPP have, in contrast to adolescents with GID, increased bone mass (for age) because of the exposure to sex steroids at a younger age. They are losing bone mass during treatment with GnRH analogs, but in the long term, bone mass is in the normal range (Poomthavorn, Suphasit, & Mahachoklertwattana, 2011). Adolescents with GID have, in principle, a normal bone mass for their age. GnRH analogs may intervene with the physiologic accretion of bone during puberty. Therefore, we examine the patients' bone development on a regular base. Data from about 120 patients showed that, at start of the treatment, all had a bone density in the normal range. Surprisingly, the MtFs had relatively lower normal values, which may be the result of a more sedentary way of life compared to the reference boys. During GnRH analog treatment, bone mass increased gradually in the young patients, while slightly decreasing in the relatively older adolescents. During cross-sex hormones, bone density appears to catch up comparably to the increase in physiologic puberty (Van Coeverden et al., 2002). The best results for bone mass at the end of the treatment protocol are seen among patients who started with suppression of puberty at a young age and thus in early puberty.

In conclusion, although in CPP a significant decrease of bone mass is seen during GnRH analog treatment, we observed, during the long-term treatment of adolescents with gender dysphoria, a continued increase of bone mass. During cross-sex hormones, a catch-up of bone accretion is seen comparable with the normal physiologic increase.

10.4.3 Metabolic Aspects

During physiologic puberty, body composition changes. Especially in girls, the amount of fat mass increases and therefore the body mass index (BMI) increases. Insulin sensitivity correlates inversely with BMI (Cook, Hoffman, Stene, & Hansen, 1993). Girls with CPP show an increase of BMI during suppression of their puberty with GnRH analogs (Aguiar et al., 2006). The question arises how BMI and insulin resistance would respond to treatment with GnRH analogs in healthy adolescents with gender dysphoria. During a period of 24 months of treatment with GnRH analogs, both biologic males' and females' BMI slightly increased about 6 %, while body fat mass increased more in biologic males than females. Surprisingly, insulin sensitivity did not decrease during this period, while in both sexes, insulin growth factor (IGF-1) and sex steroids decreased. The lack of a change in insulin sensitivity on the increase of BMI may be the result of the disappearance of sex steroids during this treatment (Wouters, Schagen, Cohen-Kettenis, & Delemarre-van de Waal, 2007).

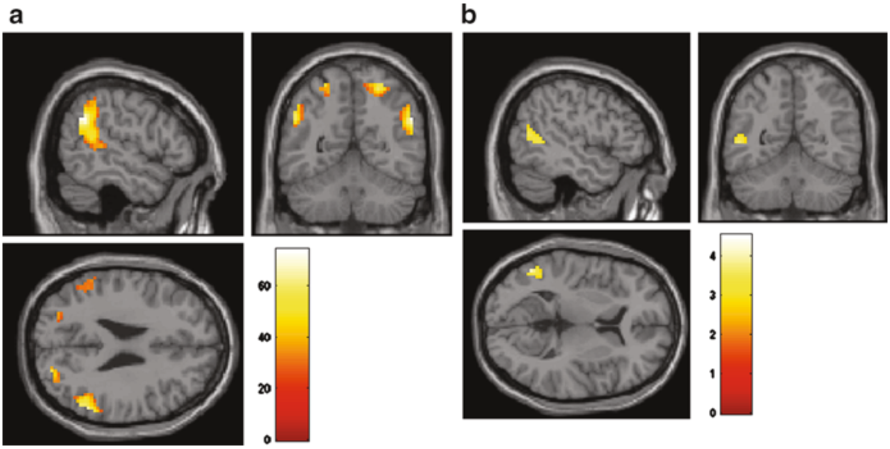

Fig. 10.2 (**a**) shows the average effect of the brain areas with increased activation during the mental rotation task. Main effects for the task are reported at $p < 0.05$ family-wise error (FWE) corrected. The threshold for cluster size is set to 10 voxels. (**b**) shows increased activation in FtM adolescents as compared to MtF adolescents in the left temporal lobe during the mental rotation task. Group by task interactions are reported as $p < 0.005$ uncorrected. The threshold for cluster size is set to 10 voxels. MRIs are performed before the start of any medical intervention

10.4.4 Brain Development

There are sex differences in brain anatomy. Significantly greater cortical thickness is observed in women compared to men, after correcting for individual differences in brain size, while no significant regional thickness increases are observed in males. Gender-specific findings support the idea of a dimorphic organization in male and female brains, which affects the architecture of the cortex (Luders et al., 2006). In addition, Zhou, Hofman, Gooren, and Swaab (1995) showed that the volume of the bed nucleus of the stria terminals (BSTc), the nucleus involved in sexual behavior, is larger in men than in women. In MtF transsexuals, they found a female-sized BSTc. The same research group also showed that men have twice as many somatostatin neurons in the BSTc as do women. In one FtM, the number of somatostatin neurons was similar to the normal male control group (Kruijver et al., 2000). These data support the hypothesis that there is a neurobiological basis of gender dysphoria.

In the Dutch adolescent gender identity clinic, we found that several neuropsychological tests concerning verbal performance, emotion, and mathematics were performed in accordance to the desired or experienced gender. For verbal fluency, MtFs produced more words than control boys and even more than FtMs and control girls (Soleman et al., 2013). Comparisons of brain activity in an fMRI design between control boys and girls showed more activation in the boys in the right Rolandic operculum, a small area adjacent to Broca's area. No significant differences were found comparing transsexual adolescents, although sub-threshold activation was found in the right Rolandic operculum, indicating a trend-wise increase in activation from control girls, to FtMs, to MtFs, and to control boys (Schagen et al., submitted). For the mental rotation test, a higher performance as well as increased activation of the sulcus parietalis was found in control boys compared to girls, as well as in FtMs than in MtFs (see Fig. 10.2a, b).

In conclusion, there are increasing data available supporting the paradigm that gender dysphoria has a neurobiological basis. The origins, however, remain unknown, but (placental) steroids and growth factors may play a role.

10.5 Conclusions Regarding the Dutch Protocol

To date, the experience of more than 10 years with this protocol in the management of adolescents with gender dysphoria, as indicated above, has not revealed complications. The patients reported satisfaction with regard to suppression of puberty and reported no regrets after treatment. However, some patients consider the age of 16 too late for the start of cross-sex hormones. In addition, in young patients diagnosed to be gender dysphoric, we have to wait until the first signs of puberty appear.

The question arises whether in cases with a long-standing diagnosis of childhood gender dysphoria the treatment can be started at the onset of puberty based on skeletal age, endocrine evaluation, and the earliest signs of puberty (budding of the nipple in girls and testicular growth in boys).

Primum non nocere (Hippocratic Oath), “at least do no harm,” may be applied to this group of patients in whom the diagnostic value of puberty in distinguishing between desisting or persisting gender dysphoria is deemed less relevant. In the future, starting medical treatment at the onset of puberty to suppress endogenous puberty while adding cross-sex hormones soon thereafter may be considered. Then the gender dysphoric patient can have a more physiologic pubertal development consistent with the typical timing of the experienced gender.

10.6 Future Perspectives

The Dutch experience on management of young transsexuals is very satisfactory for the patients, their parents, and their environment. However, adjustment of the interventions we use now may improve both physical and mental aspects. At the moment, earlier intervention is obstructed by the fact, among other things, that there is not any hard diagnostic tool to determine whether the patient has persisting gender dysphoria and is a good candidate for gender reassignment. Although it is doubtful that such a tool will become available, hopefully better indicators will be developed in the future.

On the other hand, the good results we have now with this protocol may give us the confidence that psychological assessment is the best diagnostic tool at the moment. Today we do not have any regrets in our young patient group. This may result from being too strict in deciding who is eligible for puberty suppression and who is not, and thereby, we may miss patients that could benefit from treatment. Since the first step of suppression of puberty is completely reversible, we may recommend starting earlier, right at the onset of puberty, rather than waiting until pubertal Tanner stages 2–3. In addition, we may start with cross-sex hormones earlier so that we mimic a completely opposite desired pubertal development at an age that is comparable to the average age of "physiological" puberty and with a typical "physiologic" progression.

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Chapter 11
Medical Treatment for Children with Gender Dysphoria: Conceptual and Ethical Issues

Simona Giordano

Abstract There are various treatment approaches available for children and adolescents with gender identity disorder (GID). This chapter offers an overview of these, with a focus on bringing to light their underlying assumption and treatment goals. After such an account, the chapter focuses on the combined approach, which involves early medical treatment for children and adolescents with GID. This treatment has raised and may raise important ethical and legal concerns: this chapter disentangles and analyzes such concerns. The conclusion is not only that there is nothing unethical with providing transgender children and adolescents with early medical treatment but that it may be unethical not to do so.

11.1 Introduction

In this chapter, I discuss the treatments that can be offered to children and adolescents with so-called gender identity disorder (GID) and the conceptual and ethical issues that these treatments present. I use the terms "children and adolescents" in a deliberately undetermined way. Children may achieve puberty at different ages, and given that there is not a clear demarcation line between childhood and adolescence, I will use the two terms to refer to the category of minors who may apply for, and be eligible for, early medical treatment.

There have been, and there still are, different treatments available for transgender minors; not all of these involve medical interventions. The differences among these treatments often reflect underlying theoretical assumptions and treatment goals.

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I will provide an account of these approaches and then analyze the ethical issues surrounding medical treatment for gender dysphoria in children and adolescents.

For the sake of clarity, I will make explicit my assumptions here: transgenderism is not to be regarded as pathological or psychopathological (Giordano, 2012). For this reason, I will tend to use the terms transgender children, gender minorities, children with gender dysphoria, or atypical gender over the psychiatric classification of GID (it should be noted that the next edition of the Diagnostic and Statistical Manual of Mental Disorders—DSM-5—due to be published in 2013, amending the term GID in gender dysphoria) (APA). It follows that attempting to “correct” atypical gender identification by seeking to align perceived gender with the gender of assignment is typically not a legitimate goal of healthcare intervention. *Successful* therapy is the one that helps the sufferer to achieve a quality of life that is good *for him/her*, or to minimize his/her suffering, whatever the preferred gender/s may be.

11.2 Brief Overview of Therapies Available

11.2.1 Behavioral and Psychoanalytic Therapies

One of the first approaches used with children with atypical gender identity development has been behavioral therapy. Through negative and positive reinforcements, behavioral therapy aims to reduce cross-gender identification. This therapy has received a vast amount of criticism: it implies that cross-gender behavior is a type of deviance and that it is good to try to amend it. Moreover, behavioral therapies for transgender people proved to be largely unsuccessful [for further details on this approach, see Moller, Schreier, Li, and Romer (2009)].

More used, but no less controversial, have been psychoanalytic therapies. Freud argued that sex and gender identity become stable with the resolution of the Oedipus complex (sometimes called Electra complex for girls).[1] The resolution of these conflicts leads the child to identify with the same sex parent. At this point, the child acquires a stable sex and gender identity. If this process is inhibited by traumatic experiences, sex and gender identification are likely to be hindered. Therefore, when people show problems in sex and gender identification, according to Freud’s theory, it is highly likely that the Oedipus complex has not been resolved appropriately (Roberts, Brett, Johnson, & Wassersug, 2008).

The Freudian theory of sex and gender development has been widely criticized. Golombok, in particular, noticed that gender identification occurs in children much earlier than the stage at which Freud postulated the resolution of the Oedipus complex to occur. Moreover, children raised in atypical families—in fatherless settings, for example, or brought up by gay or lesbian couples—have a sex and gender identification that is comparable to those raised by one woman and one man (Golombok, Cook, Bish, & Murray, 1995; Golombok & Fivush, 1994; Golombok, MacCallum, & Goodman, 2001; Golombok, Murray, Brinsden, & Addalla, 1999; Golombok, Spencer, & Rutter, 1983; Golombok, Tasker, & Murray, 1997). If gender identification depended on the resolution of the complexes hypothesized by Freud, this would be highly unlikely, if not impossible.

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[1] Electra is another mythological figure in ancient Greece, which inspired various works, the most famous of which are probably the tragedies *Electra* by Sophocles and Euripides. Here, Electra plans the murder of her mother’s lover, who killed her father. Sometimes the term “Oedipus complex” is also used for girls.

Despite the fact that Freud's interpretation of gender development has had limited success, the (perhaps more raw) idea that transgenderism results from situations of family conflicts that the child elaborates through rejection of their gender of assignment has instead had more traction. There is, however, no evidence that transgenderism is monocausal or that upbringing has a large role in its development (Gaffney & Reyes, 2009).

It should be noted that, within the traditional psychoanalytic framework, *successful* therapy is the one that brings the person back within the binary *male or female* polarity. There has been a proliferation of cases in the literature allegedly "cured" with psychoanalysis. The assumption in these cases is that, structurally, the development of gender, when appropriate, will lead a child to mature into a man or into a woman, in a stable way across time, depending on the biological sex, provided that the family is functional enough to promote *adequate* adjustment (Haber, 1991).

The model does not account for the fact that biological sex itself is not straightforward; according to some researchers, there are not two but at least four or five sexes in humans [for a review of the literature on this research, see Giordano (2012)]. Moreover, in considering gender variance as pathological, at the best as an adaptation to a dysfunctional setting, this approach assumes what needs to be demonstrated (that transgenderism is indeed pathology) and risks basing clinical practice on this unsubstantiated assumption.

Of course, any therapy, and not just psychoanalysis, will have underlying assumptions relating to what a good life is, to what the good for the individual is, or to how it should be understood. However, it is desirable that the assumptions and goals be made explicit in order for patients to be able to make an informed choice as to whether or not they can share them, or, eventually, negotiate assumptions and goals that are agreeable to them. Unless there is an alignment of values between the healthcare professional and patient, it may be difficult to assess therapeutic "success."

There are several types of psychotherapies available, in addition to psychoanalysis, and psychotherapy is invariably advised for (and requested by) patients with an atypical gender identity development who want to transition. However, psychotherapy alone does not seem to offer sufficient help to transgender people, including children and adolescents (Kreukels & Cohen-Kettenis, 2011). Whereas there is high emotional distress in these children and higher levels of anxiety are noted than in control groups (Wallien, Van Goozen, & Cohen-Kettenis, 2007), it is now more frequently acknowledged that emotional distress is a consequence of their gender identity rather than its cause (Moller et al., 2009). Usually transgender children will need a broader range of interventions, other than psychological support, in order to express more fully who they are and thus to achieve a satisfactory quality of life.

11.2.2 Etherapy and Distance Counseling

Online therapy (e-therapy) and distance counseling may counteract the isolation and marginalization that some transgender people may experience, especially in areas in which specialized healthcare provision is lacking. However, there is insufficient evidence to establish the advantages and disadvantages of this approach for this category of patients. Some of the possible advantages and risks are discussed in the Standards of Care published by the World Professional Association for Transgender Health (Coleman et al., 2012).

11.2.3 Combined Approach

A combined approach includes administration of medical therapies as well as psychotherapy, social intervention, and family work (Cohen-Kettenis, Delemarre-van de Waal, & Gooren, 2008; De Vries & Cohen-Kettenis, 2012; Di Ceglie, 2009). The main aim of this approach is to alleviate distress and improve the child's quality of life and not to reduce cross-gender behavior or realign the child's perceived gender with the gender of assignment. Combined therapy for gender dysphoria includes three stages:

1. Stage 1: Fully reversible interventions (administration of medical therapies that suspend pubertal development) (Wylie, Fung, Boshier, & Rotchell, 2009).
2. Stage2: Partially irreversible interventions (administration of masculinizing/feminizing hormones).
3. Stage 3: Irreversible interventions (surgery) (Green, 2007).

I will focus on Stage 1, as it involves the administration of medication to minors and as it has raised acute ethical and legal dilemmas (Houk & Lee, 2006). I will concentrate on the ethical issues surrounding early medical treatment, but, where pertinent, I will offer some considerations relating to the laws regulating the treatment of minors, as these may apply to our case. These laws are likely to vary significantly in different countries, and my focus will be on the law in England and Wales, but this may provide one example of a set of answers to some of the pressing issues arising during the clinical encounter between a transgender minor and healthcare professionals. A fuller analysis of the legal issues has been provided elsewhere (Giordano, 2012).

11.2.4 Stage 1 Treatment: A Brief Description

The first stage of treatment generally involves the administration of drugs that cause a temporary suspension of pubertal development. This treatment, where provided, is offered in cases in which gender dysphoria is diagnosed as profound and highly likely to persist. The endogenous production of estrogen in girls and testosterone in boys is temporarily suppressed. Gonadotropin-releasing hormone analogues (GnRHa) are the most effective available drugs, subject to a range of caveats that I shall sketch in a moment. GnRHa act on the pituitary gland and inhibit the pituitary hormone secretion.[2] These drugs are sometimes called "blockers." These could be given to early adolescents just after the onset of puberty, before the substantial development of secondary sex characteristics. This is around what is known as Tanner Stage 2 or 3 (Marshall & Tanner, 1969, 1970). During the first and second stage of treatment, some children will have what is sometimes called a real-life experience (Levine, 2009). This involves adopting the role of the other gender in order to experience the congruence with presumed innate gender identity. During the first stage of treatment, the child normally also receives psychological support. Sessions with the psychologist are meant to help the patient make a conscious and thoughtful, well-informed decision as to whether or not to proceed with the actual first step of gender reassignment, cross-sex hormones. The child/adolescent might decide to transition and eventually to later begin cross-sex hormones. Alternatively, she/he may wish to revert to the gender of assignment and interrupt therapy. By resuming the endogenous sex hormone production, the pubertal development is thought to restart as normal. For this reason, blockers are regarded as a *reversible intervention*.

Puberty-suppressing drugs can be regarded as, at least to some extent, a *diagnostic tool*, as one of their most important functions is to enhance understanding of the nature, degree, and persistence of the child's discomfort (Cohen-Kettenis, 1998; Delemarre-van de Waal & Cohen-Kettenis, 2006).

11.2.5 Stage 1: Benefits and Risks

Temporary suppression of pubertal development has the following advantages:

1. It immediately reduces the patient's suffering (Cohen-Kettenis & Pfäfflin, 2003).
2. It improves the precision of the diagnosis. Adolescents are given more time to explore their self and their gender, without the distress of the changing body (Cohen-Kettenis & Pfäfflin, 2003).

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[2] I am grateful to Professor Mike Besser for this specification.

3. It can also help identifying children who are false positives (Delemarre-van de Waal & Cohen-Kettenis, 2006).
4. It reduces the invasiveness of future surgery. In female to male, it would avoid, for example, breast removal; in male to female, it would avoid painful and expensive treatment for facial and body hair; moreover, the voice will not deepen, and the nose, jaw, and cricoid cartilage (Adam's apple) will be less developed. This will avoid later thyroid chondroplasty to improve appearance and cricothyroid approximation to raise the pitch of the voice (Cohen-Kettenis & Pfäfflin, 2003).
5. Better psychosocial adaptation appears to be associated with early physical intervention (Cohen-Kettenis & Pfäfflin, 2003). "Early intervention not only seemed to lead to a better psychological outcome, but also to a physical appearance that made being accepted as a member of the new gender much easier, compared with those who began treatment in adulthood" (Kreukels & Cohen-Kettenis, 2011).

With regard to the risks, a major concern is the impact of GnRHa on development. Administration of GnRHa slows the pubertal growth spurt. This can represent an advantage for male to female children, as it makes it more likely for them to achieve an ultimate height within the normal female range. However, the obvious question is whether reduction of the rate of growth has any side effects on bone formation and metabolism (Haraldsen, Haug, Falch, Egeland, & Opjordsmoen, 2007). GnRHa inhibit the production of endogenous sex hormones and thereby impact on the bone mass growth. Later administration of cross-sex hormones can increase bone mass, but long-term effects on bone mass development and sitting height are unclear. Data thus far provided by the Departments of Medical Psychology and Pediatrics in Amsterdam show that later administration of cross-sex hormones makes it possible to manipulate overall height and achieve *quasi* normal height (Cohen-Kettenis & Delemarre-van de Waal, 2005).

Another concern is the effect of GnRHa on the brain. Males and females show different brain development, especially in the amount of gray matter. There is now ample evidence that brain maturation continues well into adolescence; however, the exact role of pubertal sex hormones in this process remains to be discovered (Delemarre-van de Waal & Cohen-Kettenis, 2006; Kreukels & Cohen-Kettenis, 2011).

Additional concerns regarding blockers are their effects on reproductive capability. Specialists in Belgium have explored these effects (De Sutter, 2009). The use of GnRHa in early puberty might prevent the storage of sperm (for male to female children) and of ova (for female to male children) for future reproductive purposes. However, spermatogenesis in males can be restored by interrupting treatment. A boy whose puberty has been suppressed before spermatogenesis has occurred could decide to stop treatment long enough for spermatogenesis to start, once he is a bit older, if he wishes to collect and store sperm for reproductive purposes (this of course would mean that he would have to accept the masculinizing effects of endogenous testosterone on his body). He can then continue with treatment for transition to female gender.

In female to male patients, ova may be collected and stored at the time of oophorectomy. The collection of ova has little impact on the already formed ova, but it is still not clear what the fertility success rates may be. Male to female patients do face an additional problem in that the genital tissue available for the later creation of a vagina will be less than would otherwise have been, if puberty is suppressed early, but this problem could be resolved with appropriate surgical intervention (Coleman et al., 2012).

Because of the potential risks of these medications, there has been a controversy internationally on the time at which medical treatment should be initiated. Some clinicians insisted that patients should wait until puberty was well on its way, or even completed. This seemingly "cautionary" approach, however, had the important disadvantage of denying transgender people the important benefits of early treatment (see above). In addition to this, Fenner and Mananzala (2005) make further considerations relating to the risks of *not receiving treatment*:

> First, it [being rejected at clinics …] alienates [sufferers] from medical providers […]. Because of this increased distrust, many may not return for primary care, HIV testing, STD treatment and other essential care […] These denials also create a necessity […] to seek this care out elsewhere. For many, this care is the only way to express their gender fully so that they can seek employment, attend school, and deal with every day interactions in their new gender. […] For many young people [medical treatment] feels like a life or death need, and they will do whatever is necessary to get this treatment. Many, when rejected at a clinic […], buy their hormones from friends or on the street, injecting without medical supervision at dosages that may not be appropriate and without monitoring by medical professionals. This opens them up to high risk for HIV, hepatitis, and other serious health concerns. Additionally, many youth have difficulty raising money to buy these hormones illegally because they do not have parental support for their transition and face severe job discrimination as young transgender applicants. For many, criminalized behaviour such as prostitution is the only way to raise the money. Doing this work makes them vulnerable to violence, trauma, HIV, and STD infection, and entanglement in the […] justice system (Fenner & Mananzala, 2005).

The clinical evidence gathered so far shows that for children with serious and persistent gender dysphoria, the best outcome is provided by starting treatment with puberty suppressant medications as soon as pubertal changes occur, at Tanner Stage 2 or 3. International clinical guidelines provide similar advice (Houk & Lee, 2006; Imbimbo et al., 2009; Moller et al., 2009; Murad et al., 2010). The reaction to pubertal changes is still used to assess the extent and persistence of the child's gender variance, and thus, a delicate balance needs to be drawn between making an accurate diagnosis and ensuring that no preventable harm is inflicted to the children by waiting too long.

The debate on early medical treatment has raised important ethical questions and has revealed weighty ethical concerns. It is to those that I now turn.

11.3 Ethical Concerns: Playing God or Fiddling with Nature?

Intervening in the spontaneous development of puberty may seem morally unacceptable—as *playing god* or as interfering (where the interference is perceived as inherently undue) with "nature."

This objection is problematic for a number of reasons, not the least of which is that "playing god" would of course only be considered by either those who believe in god or the agnostic. Perhaps more importantly, those who use this line of reasoning should provide a cogent account of what they mean by "nature." But even leaving aside these terminological and conceptual problems, the appeal to "nature" (which I use in inverted commas due to its vagueness) still fails on other grounds.

Firstly, it is not clear why "natural" developments should not be interfered with, when the purpose of the interference is to alleviate suffering or ameliorate people's lives. Medicine, and perhaps the whole apparatus of science and without exaggeration probably the whole of human knowledge, aims at understanding better and hopefully ameliorating the *status quo*, the allegedly "natural" course of events. Many of the choices and actions that most people would reasonably regard as morally decent have a similar purpose: stopping our children from running into incoming traffic is an interference with "nature," and so it is to call an ambulance if we saw a person in need. One cannot coherently argue that any similarly decent behavior, aimed at preventing or reducing the ill health or misfortunes that "naturally" occur to our fellows and to ourselves and which indeed represents interferences with the "natural" course of events, is immoral without proving that the most basic moral attitudes, like compassion and desire to prevent harm, are utterly deplorable or wicked. David Hume, in an essay published in 1783, wrote:

> If I turn aside a stone which is falling upon my head, I disturb the course of nature, and I invade the peculiar province of the Almighty, by lengthening out my life beyond the period which by the general laws of matter and motion he had assigned it … any why not impious, say I, to build houses, cultivate the ground, or sail upon the ocean? In all these actions we employ our powers of mind and body, to produce some innovation in the course of nature; and in none of them do we any more (Hume, 1783).

The appeal to god or "nature" has a long and not praiseworthy history. John Stuart Mill, for example, pointed out how the appeal to "nature" was used in his times to justify the subjection of women as well as the subjection of black people in America. Women were regarded as "naturally" suited for domestic roles, black people as "naturally" inferior, and the appeal to "nature" was used in the attempt to justify what was, effectively, slavery in both cases. The idolatry of "nature" has been used ad hoc in the attempt to justify various forms of violence or to deny important goods to others.

Secondly, doctors interfere with "nature," or, more precisely, with spontaneous developments, all the times, and we all do. Doctors treat people in the hope of delaying death, and thus they, rightly so, unscrupulously interfere with the course of "nature." Malignant tumors are spontaneous developments, which doctors treat routinely, and no serious objections are raised against governments that fund cancer research.

One may object that comparing cancer with puberty is preposterous: illnesses are not "spontaneous" developments in the same way that pubertal development is. This objection does not account for what a "spontaneous pubertal development" may mean to a transgender child. Developing in a body that is perceived as alien is simply not an option for many transgender children; the sequel associated with puberty is grim for many transgender children, and some would rather take their life than develop in the "natural" body (Fenner & Mananzala, 2005). For these children, the spontaneous development of puberty is no less fatal than a malignant illness. In fact, this objection assumes that some processes are "illnesses" and others are not. From this epistemological claim, the objection draws normative conclusions, such as that it is ethical or even obligatory to interfere with illnesses and unethical to intervene with "natural" developments. But the epistemological assumption is not valid, and neither are the normative conclusions justified. How people define what is a disease, an illness, an abnormal state, a disadvantaged state, and an unbearable state is open to serious debate (Symposium on Disability, 2001).

Any epistemological claim that some conditions are "spontaneous" or "natural" or "normal" and others are "illnesses" should be explained, especially when the purpose of the epistemological claim is to deny people important benefits that they claim for themselves.

But even if a convincing definition of what "illness" is and is not could be provided, the normative implications proposed do not logically follow. Ageing is associated with various adverse effects on our health, yet it is not generally regarded as wrong to interfere with this process of spontaneous development in order to ameliorate people's quality of life. Or should doctors refuse on ethical grounds to prescribe calcium or estrogens to postmenopausal women to counteract the spontaneous bone mineral density loss? Should hip replacements be banned on moral grounds? Should fitness instructors on ethical grounds refuse to prescribe weight-bearing exercise to older clients with osteoporosis? Would we be morally repugnant if we exercised in order to delay the spontaneous process of ageing?

If it is right to intervene to delay ageing at one end of "spontaneous development" (towards the end of life), to ameliorate a person's quality of life, or to minimize his/her suffering, it should be right to delay ageing at the other end (towards its beginning) for the same purposes.

One could here object further that, even if it is "natural," ageing causes tangible hideous effects on one's health and safety. So, the objection may go; it is not ageing per se that doctors interfere with but the illnesses associated with it. Giving pubertal suppressant medications is instead an interference with the development per se, and not with its hideous effects.

This objection does not stand up to close scrutiny. It is unclear how one can logically or practically separate an interference with ageing per se from an interference with its effects. Coronary bypass artery surgery, for example, is likely to delay death and thus affects both the process of ageing and the diseased organ. Conceptually separating ageing per se*,* the spontaneous (and allegedly benign) process, from the hideous effects of it, seems patent nonsense. More importantly, it is obviously true that ageing usually carries with it adverse effects on people's health and that people who age may suffer age-related diseases: but who says that a transgender child suffers less than a person with osteoarthritis? Or should doctors be invested with the power of deciding whose suffering deserves alleviating?

It may be easier for many of us to relate to the suffering of an ageing person than to the suffering of a transgender person, simply because many of us will age, and only a few of us will experience gender dysphoria. But the suffering that we are unlikely to experience ourselves is not for that reason less painful to the ones concerned or less worthy of our own concern.

Insofar as interference with what is thought of as a "spontaneous" or "natural" development is likely to alleviate suffering and promote well-being, there is a strong prima facie reason in favor of interfering.

11.4 Is It Unethical to Make Choices That Affect the Future of a Child?

Having established that it is not *interfering* per se that is unethical, it may be further argued that gender identity development is a complex and still scarcely understood process, and some healthcare professionals may be reluctant to interfere medically with it because of the long-term unforeseeable consequences that this may have. Some may wonder whether, without medical treatment, the child may eventually feel comfortable with his/her body.

In addressing these concerns, we should first note that many types of interventions (not only medical) in the life of a child represent important interferences with his/her future. Sending them to school, raising them as a part of one culture or religion, and many others are choices made at a certain point in time that produce long-term consequences: they open up some options and foreclose others. Not taking any action also interferes with the person's future: for example, not sending our children to school also has long-term consequences. Sometimes worse consequences result from taking *no action*. Indeed, it could be argued that there is no such a thing as *no action* and that any choice, including the choice not to intervene, is still *doing something*. From this point of view, refusal of treatment is not simply *taking no action* but making a choice that has consequences. This explains why in some countries deciding not to treat can be an offense (omission of treatment).[3]

A decision (in our case, to treat or not to treat, to treat in a determined way at a certain point in time or in a different way later) finds its moral justification in the foreseeable consequences that that decision is likely to produce. The choice with the best foreseeable consequences for the patient is, prima facie, the one to be preferred. Of course, a forecast of the foreseeable consequences is open to failure: nobody (doctors are no exception) can see into the future. It is, for example, possible that we judge early treatment as beneficial for a particular child and that that child is a "desister" that she/he decides to interrupt therapy; it is even possible that gender dysphoria would have subsided spontaneously even without treatment. It is thus possible that some of those whose dysphoria has subsided *after* the initiation of treatment might have been "desisters" anyway, even without treatment. It would be impossible, however, to know whether in these cases the treatment and support received has helped those allegedly false positives to adapt to their gender or whether they would have adapted in the same way without treatment. In fact, "desisters" may also benefit from early treatment. Early suspension of puberty may allow the child the time to explore his/her gender without the fear of growing in the "wrong" body and may actually *prevent* the later provision of more irreversible treatments (such as hormones) to false positives. If treatment is withheld, instead, or postponed, the child who is a "persister" will incur certain and preventable harm. This means that, whereas in other situations it may be prudent to defer medical treatment until the child is older, delaying treatment of even a few months in cases of gender dysphoria may have hideous consequences.

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[3] In Italy, for example, Articles 328, 591, and 593 of the Penal Code, respectively, *Omission or Refusal of Official Acts*, *Abandonment of the Incapacitated*, and *Omission of Rescue*.

One could ask whether it is possible that some of the children who receive early treatment may proceed to transition and whether, if they were not treated at all, their condition may have subsided spontaneously. This less appealing possibility is quite remote as, where early treatment is provided, this follows a careful selection process and careful diagnosis. Early treatment is offered to children who suffer significant distress and who manifest strong and persistent dysphoria; their progress and levels of satisfaction are monitored carefully over time, before more irreversible treatments are provided.

Certain forecasts are outside the boundaries of medicine: medicine is about probabilities, not indisputable deductions. Thus, the only way in which doctors and patients can proceed is to balance probabilities and evaluate likely outcomes, both on grounds of careful assessments of each individual patient and of the evidence available.

11.5 Who Decides on What Is in the Best Interests of a Patient?

Whereas the best interests of patients should in principle be served, doctors may still wonder how these should be understood and who should make a judgment. There is a wide agreement that medical decisions regarding children should promote their welfare. For example, the British Medical Association (BMA) states: "The welfare of children and young people is the paramount consideration in decisions about their care" (BMA, 2011). In England and Wales, Section 1 of the Children Act 1989 states that the welfare of the child must be the "paramount consideration."[4]

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[4] Online at http://www.legislation.gov.uk/ukpga/1989/41/section/1. Last accessed 15 November 2011.

In English jurisprudence, it has been established that best interests are not to be regarded narrowly as *medical* interests only, as previously understood.[5] Best interests must encompass ethical, social, moral, emotional, and welfare considerations.[6] In *A Hospital NHS Trust v. S and others,* it was stated: "When considering the best interests of a patient, it is […] the duty of the court to assess the advantages and disadvantages of the various treatment and management options, *the viability of each such option and the likely effect each would have on the patient's best interests and, I would add, his enjoyment of life* […] any likely benefit of treatment has to be balanced and considered in the light of any additional suffering the treatment option would entail"[7] (my emphasis). The professional's opinion needs to be *reasonable and responsible*; has to have a logical basis, it has to be grounded on an evaluation of the comparative risks and benefits and must be defensible.[8] Doctors are not the sole judges of the patient's best interests.

When it is not immediately evident what is in a patient's best interests, or when there is a dispute between the parties (e.g., the family and patient on the one hand and the healthcare professionals on the other), in England it will be up to the courts to determine the patient's best interests and no longer up to the doctors alone. The judgment will be made according to the established view that best interests encompass not only medical interests but also the person's present and past feelings, wishes, beliefs, and values. In all cases, and thus in cases of younger minors as well, best interests will be assessed in light not only of medical evidence but also of the nonmedical evidence relating to the patient's overall condition. In the UK, the General Medical Council (which, it should be mentioned here, is not the law in the UK) also states that the child's best interests are not confined to clinical interests but include, among other factors, the views and values of the child, of the parents, and an evaluation of the choice, if there is more than one, which will least restrict the child's future options (GMC, 2007).

These provisions may set out principles that can guide the judgment of clinicians in the interaction with transgender minors. Doctors are not clairvoyants: all that can be expected of them is to make a careful assessment of each individual applicant, by involving, wherever possible and appropriate, the family, in order to understand the history and the extent of the child's discomfort and to make a prediction that is as accurate as possible of how the child will feel if treated and if not treated, based on the facts available at the time. In the clinics that adopt a combined approach, generally the child is seen by a team of specialists, as gender dysphoria encompasses endocrinological, psychological, and social issues. (It should be noted that WPATH in 2011 has taken a flexible approach and contemplates the possibility that individual healthcare professionals be involved with patients with gender dysphoria.)

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[5] *Bolam v. Friern Hospital Management Committee* [1957] 2 All ER 118, [1957] 1 WLR 634.

[6] *A v. A Health Authority* [2002] 1 FCR 481, [2002] Fam 213 at para 43; see also *Re A (medical treatment: male sterilisation)* [2000] 1 FCR 193; *A Hospital NHS Trust v. S and others* [2003] Lloyd's Rep Med 137, (2003) 71 BMLR 188 at para 47.

[7] *A Hospital NHS Trust v. S and others* [2003] Lloyd's Rep Med 137, (2003) 71 BMLR 188 at para 47.

[8] *Bolitho v. City and Hackney HA* [1998] AC 232 at 242, HL.

WPATH also allows for individual health professionals to adapt the clinical guidelines to suit the needs of the individual patient. These departures, WPATH warns, should be recognized as such, explained to the patient, and documented through informed consent (Coleman et al., 2012). If the specialists, after careful evaluation, regard the dysphoria as strong and likely to persist, and if deferring treatment seems on balance of probabilities the most risky option, then there are grounds for considering early treatment as being in the best interests of the child. Determination of best interests should also be based on best available clinical evidence and on published research (evidence-based medicine). If healthcare professionals assess the child's best interests in this manner and it appears that initiating treatment seems, on balance, in the best interests of the particular child, they should be able to commence treatment and their conduct will be most likely irreprehensible.[9]

11.6 At What Age Can Children Decide?

The age at which a child may participate directly in the therapeutic process, and may even consent to treatment without the knowledge of their parents, will be regulated by the laws in force in each individual country. In England and Wales, minors aged 16 and 17 have a right, as stated by the Family Law Reform Act 1969, to consent to medical treatment. For those below the age of 16, the famous case known as *Gillick* would apply. The court in that case established that a child under sixteen can give an effective consent to medical treatment, provided that she/he had reached "sufficient understanding and intelligence to be capable of making up his own mind in the matter requiring decision."[10] This is known as the *Gillick* test, or *Gillick* competence test. Generally, the more serious the decision, the greater the capacity required of the minor.[11] It should be noted that if the treatment is offered only within a research study, *Gillick* may not apply [for more see Giordano (2012)]. Should parents oppose treatment that is deemed to be in the best interests of the child, the consent of the child who has *Gillick* capacity is normally valid in England. In any case, it should be borne in mind that, even with young minors or infants, parents, or those with parental authority, in England do have a right to make decisions on behalf of their children only insofar as their decision is not detrimental to the child's best interests; for example, Jehovah's witnesses do not have a right to refuse whole blood transfusions on behalf of their children. Should the parents' decisions be detrimental to their children's best interests, these decisions can be overhauled.

The legal provisions relating to consent in minors are likely to vary significantly in different countries. However, it is generally recognized that the child's capacity to consent to medical treatment "does not depend on the age of the child, but on subjective features of the child in respect to the particular treatment proposed" (Jones, 2006). The British Medical Association (BMA) states:

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[9] *Re J* (A Minor) (Child in Care: Medical Treatment) [1992] 2 All ER 614.

[10] Gillick v. West Norfolk and Wisbech Area Health Authority [1985] 3 All ER 402 at 409 e-h per Lord Fraser and at 422 g-j per Lord Scarman; See also R v. D (1984) 2 A11 ER 449.

[11] *Re S* (A Minor) (Consent to Medical Treatment) [1994] 2 FLR 1065; *Re E* (A Minor) (Wardship: Medical Treatment) [1993] 1 FLR 386.

Children and young people can expect:

- To be kept as fully informed as they wish, and as is possible, about their care and treatment.
- Health professionals to act as their advocates.
- To have their views and wishes sought and taken into account as part of promoting their welfare in the widest sense.
- To be the individual who consents to treatment when they are competent to do so.
- To be encouraged to take decisions in collaboration with other family members, especially parents, if this is feasible.
- To be able to expect that information provided will remain confidential unless there are exceptional reasons that require confidentiality to be breached (BMA, 2011).

In international documents, similar points are made. For example, the Convention on the Rights of the Child, adopted in 1989 by the UN General Assembly, states that the child has a right to have his/her views accorded due weight in relation to the child's maturity (UNICEF, 1989, Article 12).

Thus, whereas the laws in different countries may diverge, it is an important principle of ethics and good clinical practice that children are not automatically assumed to lack capacity and that a therapeutic relationship be based on taking seriously into consideration the child's opinions about his/her own care. Including children in the therapeutic process should be the norm, and they should not be regarded as incompetent just because they do not agree with the physicians. Importantly, doctors should not judge the capacity of a child solely on the basis of his/her age. Because the decision either to suspend puberty or to transition involves both significant others and others at large, it would probably be difficult for a child to initiate the process of medical treatment for gender dysphoria without support, even if she/he had the legal capacity to do so. Perhaps for this reason, international guidelines generally insist on the importance of family participation (Coleman et al., 2012). On the other hand, it must be recognized that children who apply to this medical treatment often have a long-term history of gender dysphoria and may have gained significant self-awareness, maturity, and capacity to make decisions on this subject matter.

11.7 Gender Dysphoria Is a Psychiatric Issue, Not a Medical Issue

The idea that transsexualism is a psychiatric or psychological problem, and therefore should not be treated medically, is one that has run through literature (Raymond, 1994). The literature has traditionally dealt principally with adults, but the point is one of relevance in the case of children as well. I have argued elsewhere that there are no sound epistemological grounds to regard gender dysphoria as a psychological or psychiatric disorder (Giordano, 2012). But even assuming for the sake of the argument that transgenderism was purely psychological, psychological treatment has a poor outcome. Why should doctors insist in using a form of therapy that has proven largely unsuccessful on its own? Pharmacological treatment is routinely used to treat the so-called symptoms of the many so-called psychiatric disorders, disorders for which no biological or somatic cause has been found. Lithium carbonate is regularly used to treat bipolar disorder, a psychiatric syndrome whose causes are unknown. It is not clear why, even if one assumed that transsexualism was a psychological or psychiatric disorder, transsexuals should not be treated in the same way as other "psychiatric" patients. There are further issues relating to whether gender dysphoria is appropriately regarded as a mental illness and to the goals of psychiatric interventions in general and in this specific case. For reasons of space and consistency, these cannot be analyzed here. For our current purposes, it is however important to remind that the fact that a condition is classified as a psychiatric disorder is not per se a good reason to refuse effective medical intervention.

11.8 Gender Dysphoria Is a Social Issue, Not a Medical Issue

Another objection raised against medical treatment for transgenderism is that the suffering associated with it is caused not by atypical gender per se but by questionable gender stereotypes and prejudice. A masculine femininity and a feminine masculinity are not foreseen in the sociocultural context of many Western countries, and this is why, according to this argument, nonconforming individuals end up seeking medical treatment, when they could and should, in principle, live their gender liminalities undisturbed. It is society that needs to change. By changing people's bodies, rather than society, a twofold harm results: a mutilation of individuals, who are exposed to the risks and pains of extensive surgery, and a reinforcement of the oppressive stereotypes that are the very cause of their suffering (Raymond, 1994).

Raymond (1994), for example, argues that trans-surgery is a form of sexual politics and medical treatment for gender dysphoria is akin to the Nazi's "medical" practices, and even worse than those, in that the transgender has so strongly internalized the gender stereotypes that has become willing to seek and consent to the mutilating procedures.

Indeed, social responses to transgenderism are, to a significant extent, responsible for the suffering of gender minorities. Social ostracism, bullying, or even open violence is a sadly common experience for gender minorities, and social ostracism often begins early in the life of the transgender (GIRES, 2008; Grossman & D'Augelli, 2006; Wallien, Veenstra, Kreukels, & Cohen-Kettenis, 2010): in societies in which the gender divide is less marked, transgender people suffer less (Connolly, 2003). One could indeed argue that it is society that should change and not individuals. This, in itself, appears a sound argument, but on further scrutiny, it turns out to be untenable.

This seemingly appealing claim is based in fact on a number of other, less transparently expressed, and less logically cogent arguments. Disentangling these "hidden" arguments helps us see why none of them stands logical scrutiny.

11.8.1 Transgenders Embrace the Gender Stereotypes That Are Responsible for Their Suffering

Part of the argument presented above is that when the gender dysphoric seeks medical alteration of their appearance, they are embracing the very gender stereotypes that are responsible for their discomfort. Raymond writes:

> Through hormonal and surgical means, transsexuals reject their 'native' bodies, especially their sexual organs, in favour of the body and the sexual organs of the opposite sex. They do this mainly because the body and the genitalia, especially, come to incarnate the essence of their rejected masculinity and desired femininity. Thus transsexualism is the result of socially prescribed definitions of masculinity and femininity, one of which the transsexual rejects in order to gravitate toward the other (Raymond, 1994).

This view needs to be balanced against the fact that many transsexuals seem to go well beyond the "classic" gender divide "male/female." Many transsexuals do not transition fully: many transwomen seek breast implants and leave their genitals as they are. Many live in the other gender without any surgery, and many embrace different segments of genders in their identity. The reasons for these choices may be diverse. However, by ignoring what happens to a significant segment of the trans-community, Raymond offers an account that is partial and perhaps even methodologically questionable.

Moreover, this argument does not account for the experience of children: some children express their atypical gender very early in life. At the age of 3 or 4, sometimes atypical gender is already clearly manifested. The child generally has a marked preference for toys and play, clothes, and activities that are typical of the other gender and may identify himself/herself with the other gender openly. It is difficult to speculate that at this stage the discomfort is due to the desire to conform with internalized gender stereotypes. I will come back to this later.

11.8.2 Transgender Treatment Is Responding with Medical Means to a Social Problem

The other side of the argument is that providing transgender people with medical treatment is responding with medicine to a problem that is social, and not medical, in nature. This other side of the argument is incomplete.

It is not clear, to start with, that gender dysphoria is solely or mainly a social problem, even if social responses can exacerbate the suffering significantly and may cause a whole range of additional problems for transgender people (bullying in schools, acceptance by peers, discrimination in employment, lack of clarity regarding to legal rights, and so on). Yet, studies suggest that there are important biological factors implicated in gender development, both typical and atypical. Gender identity development does not solely depend on social factors and reinforcements: biological and cognitive factors are also implicated in the process. It is, thus, at best simplistic to assume that, whereas biological factors are implicated in typical gender identity development, no biological factors are involved in atypical gender development (Giordano, 2012).

But even if there were no identifiable biological bases for gender dysphoria, this would not necessarily say much about the ethics of providing medical care. It is normal clinical practice to offer medical treatment for conditions of suffering that appear solely determined by social variables or norms (even by morally dubious social norms, as we shall see later in this chapter). Children whose growth is deemed to be retarded or excessive routinely receive endocrinological treatment[12] purely on psychological grounds (Drop, de Waal, & de Muinck Keizer-Schrama, 1998). Treatment for "bat ears" in children, circumcision in male infants and children (still legal in England), or "corrective" surgery for many forms of the so-called disorders of sex development (DSDs) are other examples of invasive medical treatment administered purely for social reasons [for an account of DSDs, see Giordano (2012)], and the list could be expanded significantly.

Of course, this raises another conceptual issue relating to how "medical conditions" can be differentiated from "social constructs," and it is possible that this is a chicken-and-egg problem. Philosophers have widely debated the issue, with unsurprisingly unsatisfactory results (Giordano, 2011). The debate has been prompted partly by disability right activists who have argued that their "different abilities" *become* "disabilities" in a given prejudicial and discriminatory social context. I will not dwell on the intricacies of this debate here: suffice it to say for the current purposes that there is no consensus as to what "an illness" is. The fact that such a consensus has not been reached has at least one important normative implication: "illness" is too vague a concept to be used as a ground for healthcare provision. It cannot be argued that what makes it appropriate or ethical to offer clinical care in one case and not in another is the fact that in one case there is an "illness" and in the other there isn't, without at least a sound and solid characterization of illness. Absent this, it must follow that, even if it were true that transgender people are to a large extent made to suffer by mistaken social stereotypes, it does not follow that *therefore* they ought not to receive medical help.[13]

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[12] I owe this important observation to Professor Peter Clayton.

[13] There might be ethical and pragmatic issues of resource allocation, which could explain why the state might not publicly fund some treatments for transgender people (or for the infertile, or for the intersex, or for the person who is dissatisfied with his/her physical appearance, and so on). However, pragmatic concerns relating to how to allocate resources and how to prioritize people's needs are not principled reasons to deny medical treatment.

11.8.3 Medicine Should Not Reinforce Bad Social Stereotypes

The other part of the argument in question is that by providing transgender treatments, the medical profession bears the responsibility of reinforcing the social stereotypes that cause transgenderism in the first place. Raymond (1994) writes: "there are many ethical objections to alleviating individual gender suffering at the expense of reinforcing, qualitatively and quantitatively, sex-role conformity."

Indeed, medical treatments that appear to reinforce social stereotypes seem dubious. Think of skin bleaching and nose filing for black people: there is something distasteful with a doctor who bleached the skin of a black woman in order to "make her more acceptable" socially or "more attractive." But, distaste apart, this raises an important ethical question: why should people, including gender minorities, be turned into martyrs of ideals? By suggesting that individuals should bear avoidable suffering because to alleviate their suffering would harm society, Raymond proposes what she reproaches the Nazis for doing: turning individuals into martyrs of the social good (of course, of one particular idea of what such a good is).

In principle, nobody should be allowed to suffer if his/her suffering can be alleviated. If this principle had to be abridged, it should be only on very stringent grounds and perhaps in exceptional circumstances. If gender minorities had to be refused medical care on the ground that their problem is social and not medical in nature, they would be jeopardized twice: once because they suffer from a social wrong in the first instance and the second time because they are denied medical care in the name of that society that harmed them.

Of course, by using the example of suspect "cosmetic" surgery, I did not wish to equate transgender treatment with skin bleaching or nose filing, neither do I wish to trivialize the suffering of people with atypical gender. I purposely raised the example of medical interventions that are clearly provided to release the stress caused solely by social stereotypes or, even prejudice, to emphasize how, even in such cases, it would be at least dubious to deny people who wanted treatment. Even more so for the transgender, whose condition is not solely caused by dubious social norms, or by beauty imperatives, but by a complex array of biological, social, and cognitive factors, which all together contribute to the development of gender.

Gender identity development is a complex process, and science has not disentangled the way in which it occurs, both in typical and atypical cases: we know that a stable gender is generally acquired around the age of 6 or 7 (Gross, 2010), that children with an atypical gender sometimes manifest this very early in childhood, and that gender identity is generally not amenable to external command. Some children may have a strong gender identification, whether or not matching with the assigned gender, very early and well before puberty; others may be unsure about their gender identity, and, in some cases, gender identity can be malleable until puberty. However, even in those cases, perceived gender identity is resilient: others will not normally be able to "convince" a child that she/he is of the gender that those others may want to attribute to him/her. This all suggests, at least, that it is not clear that the transgender person suffers solely or mainly because of mistaken social stereotypes: the discomfort may appear arguably a long time before those stereotypes are even known to the child, and a child may well oppose typical gender stereotypes.

In conclusion, the argument that transsexualism is a social problem and therefore should not be treated medically is flawed. It is not clear that gender variance is solely the product of gender stereotypes, and even if it were (a claim that cannot be substantiated given the complexities involved in gender development), this would not imply that medical treatment should not be offered. Of course, there is no reason to believe that one type of intervention (medical) should exclude others (social and familial).

Other important concerns relate to the experimental nature of pubertal suppressant medications.

11.9 Experimenting on Children Is Unethical

The administration of puberty suppressant medications is to some extent experimental. The impact of GnRHa on bone formation and its effects on the brain, as we saw earlier, is under scrutiny, and it may be questioned whether it is ethical to offer children a treatment whose side effects have not been fully established.

The ethical issue is twofold here. Firstly, one can ask whether genuine consent can be provided in cases of experimental treatment: how can a person consent to a treatment without clear information relating to the side effects? Secondly, one could ask whether, even if the person could give valid consent in the face of uncertainties, it would be ethical to expose patients, especially children, to unknown risks.

11.9.1 Can Genuine Consent Be Given to Experimental Treatments?

One of the core features of valid consent to any medical intervention is information. However, valid consent to a medical intervention can still be given even if its side effects have not been fully established—and it’s this that prevents all medical research involving human beings being unethical from the start, whether research participants are children or adults. In order to give valid consent, the patient or research participant must receive as complete information as possible about treatment and has to be informed about the potential risks and benefits, even if these risks have not been fully established. Patients should be aware that they are able to withdraw their consent to continuation of involvement with the therapy or research project, if this treatment is provided within a research protocol, and never be subjected to any inhuman or degrading treatment or avoidable and unwanted harm or injury (World Medical Association, 2008). Once all available material information has been provided, the prospective patient or research participant will consider the potential risks of treatment with its potential benefits and make a decision as to whether to consent to treatment or refuse it.

The laws of each country, as well as established international guidelines, provide clear advice as to how to ensure that valid informed consent is gathered in cases of minors who apply for innovative or experimental treatment or for participation of minors in medical research. The CIOMS guidelines, for example, have specific articles offering advice as to how to proceed with minors (CIOMS, 2002). In England, the Clinical Trials Regulation, Schedule 1, Part 4 establishes the conditions and principles of research that apply in relation to a minor. These implement in national law the Directive, 2001/20/EC of the European Parliament and of the Council on the approximation of the laws, regulations, and administrative provisions of the Member States relating to the implementation of good clinical practice in the conduct of clinical trials on medicinal products for human use, issued on the 4th of April 2001 (Directive, 2001/20/EC). Article 4 states:

In addition to any other relevant restriction, a clinical trial on minors may be undertaken only if:

(a) The informed consent of the parents or legal representative has been obtained; consent must represent the minor's presumed will and may be revoked at any time, without detriment to the minor.
(b) The minor has received information according to its capacity of understanding, from staff with experience with minors, regarding the trial, the risks and the benefits.
(c) The explicit wish of a minor who is capable of forming an opinion and assessing this information to refuse participation or to be withdrawn from the clinical trial at any time is considered by the investigator or where appropriate the principal investigator.
(d) No incentives or financial inducements are given except compensation.
(e) Some direct benefit for the group of patients is obtained from the clinical trial and only where such research is essential to validate data obtained in clinical trials on persons able to give informed consent or by other research methods; additionally, such research should either relate directly to a clinical condition from which the minor concerned suffers or be of such a nature that it can only be carried out on minors.
(f) The corresponding scientific guidelines of the Agency have been followed.
(g) Clinical trials have been designed to minimise pain, discomfort, fear and any other foreseeable risk in relation to the disease and developmental stage; both the risk threshold and the degree of distress have to be specially defined and constantly monitored.
(h) The Ethics Committee, with paediatric expertise or after taking advice in clinical, ethical and psychosocial problems in the field of paediatrics, has endorsed the protocol.
(i) The interests of the patient always prevail over those of science and society (Directive, 2001/20/EC).

Thus, whereas special caution needs to be taken, providing experimental treatment to children, or enrolling children in research, is not in principle unethical, nor it is unlawful in many countries.

11.9.2 Is It Ethical to Expose Children to Unknown Risks?

The other question is whether it may be ethical to expose people, especially minors, to unknown side effects of experimental treatments, which could affect their future, even if their consent was valid. Children and adolescents might be believed to have greater difficulty than adults in foreseeing how they will feel in the future, due to their limited capacity at long-term judgment and their more scanty knowledge of their self and because gender identity may still be fluctuating during adolescence. It may be even questioned how a child can know before the age of puberty that they are transgender: only once gender has fully developed, one may believe and may reach the conclusion that that gender is mistaken for them.

Although these concerns are understandable, children may show marked gender dysphoria well before the onset of puberty. Their perceived gender may mismatch with the assigned gender very early in life; the incongruence may continue through childhood, and by the time a child is about to hit puberty, she/he may know enough about himself/herself to make a decision as to whether she/he wishes to begin medical treatment or not. While many children with gender dysphoria will be "desisters," that is, their dysphoria will subside, for the majority of those who continue to experience it after the onset of puberty, gender dysphoria is most likely to continue in adulthood (Reed, Rhodes, Schofield, & Wylie, 2009). The evidence collected thus far shows that for children with marked and persistent gender dysphoria, early treatment is both beneficial and benign. Effects of GnRHa are reversible and, based on the data collected to date, associated with no severe or uncontrollable side effects (see earlier in this chapter). Masculinizing and feminizing hormones have effects that are more difficult to reverse; however, Stage 2 treatment should in principle be administered after Stage 1 treatment and after a careful assessment of how the child reacts to the first phase of treatment. This is an additional reason why Stage 1 treatment is so important: it may prevent the treatment of false positives, of those children who may have some gender dysphoria, but who will not transition.

On the contrary, *not being treated* early may be devastating for most children and adolescents with profound and persistent gender dysphoria, and will force those who go on to transition into unnecessary mutilating surgery and other preventable harm (see earlier in this Chapter). The certain and real side effects of *not receiving treatment* might, for many, outweigh the potential risks of this treatment (Fenner & Mananzala, 2005; Kreukels & Cohen-Kettenis, 2011). Patients, including minors, can make an informed and rational choice to take the potential risks of treatment, including those who have not been fully established, when the alternative is on balance of probabilities much worse for them. They may have sufficient knowledge of themselves to have the capacity to consent to medical treatment before puberty is well under way [for more on the determination of legal capacity in minors, see Giordano (2012)].

It may be worth reporting here another argument against early treatment that has been produced in the literature. During adolescence, it has been suggested, the ratio of gray to white matter in the prefrontal brain area changes, and there are increases in connectivity between this area and other areas of the brain, as well as an increase in dopaminergic activity in prefrontal striatal limbic pathways. These, it is argued, may lead to increased likelihood of making impulsive choices or engaging in risky behavior. It should, however, be noted that this potentially increased predisposition to impulsive choices may lead the young adolescent who does not receive medical care to engage in risky behavior out of despair. Young people who are denied medical care might try to obtain the medications through illegal sources and may even become suicidal. Moreover, the wish to change gender never occurs abruptly, and it is a long-term issue for those who eventually are referred to the specialists. It is thus highly unlikely that the wish to undergo treatment for gender dysphoria may be caused by the variations in the central nervous system suggested here (Kreukels & Cohen-Kettenis, 2011).

11.10 What Are the Responsibilities of the Doctors?

The arguments developed so far have wide implications relating to the doctors' responsibilities. In judging whether or not to treat, healthcare professionals should evaluate what is likely to happen to the person who applies for treatment if she/he does not receive treatment, and not only what is likely to happen if she/he does receive treatment. In other words, healthcare professionals should take into consideration the consequences of their omissions as well as those of their actions. This might seem to go beyond professional obligations: clinicians might feel that they must assess the clinical benefits and risks *of therapies*, but that they are not responsible for what happens to people outside their clinics. Thus, for example, they may believe that they are responsible if they administer a drug, with the result that bone development or brain development is impaired, and that they are not equally responsible if the adolescent, against his/her professional advice, gets hormones in the streets or takes his/her life, having been refused medical care.

The extent to which all of us, including healthcare professionals, are responsible for the implications of our choices further down the line, or for what other people decide to do also as a result of our own choices (here including our own omissions), is open to debate. However, it is a mistake to believe that we bear no responsibility whatsoever for any of these implications. Omitting to treat, or deferring treatment, is not a morally neutral option. Deferring treatment may mean alienating minors from healthcare services, subjecting them to preventable mutilating surgery later on, and exposing them to the risk of body dissatisfaction (they will have to bear forever with the consequences of having fully grown in a body that they perceived as alien to them) and to preventable bullying and social discrimination due to an ambiguous appearance, which could have been prevented with early treatment. In order to avoid all of this, children may feel that they have no other option but to obtain medications off the illegal market, running the risk of entanglement with street life and with the juvenile justice system (Fenner & Mananzala, 2005). Suicidal ideation and suicide attempts are much higher in transchildren who have not been able to access early treatment than in those who have been medically treated early (Spack, 2008).

Doctors, generally speaking, do not have an obligation (at least under English law) to treat just because a person wants treatment, even if that person has the capacity to consent to treatment. Healthcare professionals (similarly to many other professionals) are entitled to refuse or withdraw their services based either on moral or on clinical judgment (but we need to remember that in other countries omitting to treat can be a criminal offense) (Giordano, 2012).[14] The doctor's and patient's opinions as to whether a certain treatment is harmful or beneficial may diverge, and this may happen in the case of administration of early treatment for gender dysphoria. These are precisely the instances in which the healthcare professional should also ponder the risks and benefits of treatment versus nontreatment, because failing to act is not necessarily the safest option or a morally neutral one. When we know that if we fail to do something, the consequences of our omissions are serious and potentially fatal for others, we have a moral responsibility for those consequences.

11.11 Conclusions

This chapter has provided an overview of the available treatment for children with gender dysphoria. Clinical evidence shows that the most promising approach involves the administration of medication to children soon after the start of puberty. I have analyzed some of the most important ethical and, where pertinent, legal issues surrounding the provision of medical treatment to people with gender dysphoria, children in particular. The arguments explored in this chapter all point toward the conclusion that denying early medical care may mean exposing children to preventable harm, and thus, not only in principle is there nothing unethical about providing early medical treatment to transgender minors, but it may indeed be unethical to deny what is, for many, the only means to achieve a satisfactory life.

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[14] This legal right has some limits under English law.

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Chapter 12
Care for Adults with Gender Dysphoria

Griet De Cuypere and Luk Gijs

Abstract This chapter gives an overview of the care for adults with gender dysphoria from the last decades of 1900 until recently, with a short vision for the future. The view on the care of individuals with gender issues has changed tremendously. This evolution is described here: from a psychotic illness, through a rather strict definition of “transsexualism,” towards a broader description of gender-variant individuals. Also, the treatment has evolved simultaneously: from antipsychotic drugs, through medical treatment (hormones and surgery) of the “true transsexual” and the psychotherapeutic approach with the adult with “secondary transsexualism,” towards a variety of possible treatments and transitions (social and/or physical), determined by the preference of the individual in consultation with the mental healthcare provider. In the most recent years, the focus has been on de-psychopathologization of gender variance; on the human rights of gender-variant people; on the effect of stigmatization, discrimination, and victimization; and on ways to prevent these negative social experiences.

Although the care of individuals with gender dysphoria has improved significantly over the past 50 years, more work needs to be done. Twenty-first-century gender care described in this volume should also be more readily available in the Southern Hemisphere and the Asia-Pacific Region. In the meantime, research evaluating treatment with the continuous aim of improving the care of individuals with gender dysphoria remains an important focus.

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12.1 Introduction

Although the phenomenon of incongruence between body-sex and soul-sex (gender) has been addressed in the scientific literature since the first half of the twentieth century, it was Harry Benjamin (1885–1986), a German endocrinologist working in the USA, who started to treat gender-dysphoric persons systematically in the 1960s with hormones and recommended surgery to end their suffering. He became interested in the subject after being introduced to a young man with gender dysphoria by Alfred Kinsey (1894–1956), who did not know how to help this patient. This young anatomical man adopted the social role of a woman. It was in 1954 that Harry Benjamin, for the first time, applied the term "transsexualism" to this phenomenon, a term that still remains popular. Psychologists and psychiatrists in those days had extreme disagreements among themselves and were mostly reluctant to give consent to medical interventions promoting transition, because many of them thought these individuals were suffering from a psychotic condition. Benjamin's book "The Transsexual Phenomenon" appeared in 1966 (Benjamin, 1966), and therein the author gave the history of 100 transsexual patients he had treated, providing details about diagnosis and medical treatment. In the meantime, Green and Money published their book "Transsexualism and Sex Reassignment" in 1969 (Green & Money, 1969). Researching history, mythology, and cultural anthropology, they concluded that the transsexual phenomenon was long-standing, widespread, and pervasive. Another important professional helping persons with gender problems was Stoller, the first psychoanalyst supportive of sex reassignment and who established criteria for this medical approach. He introduced the word "gender identity," a word that remains essential in the discourse about gender diversity. Next to infant–parent relationship and the child's perception of its external genitalia, he attributed a biologic force to explain its origin (Stoller, 1968).

In the Netherlands, the first sex operation was performed in 1959. But the surgeon was brought into court! The accusation was about performing surgery on a delusional person, because transsexualism was considered a delusion. Although the surgeon was acquitted, this incident delayed systematic help and care for transsexuals in the Netherlands until the end of the 1960s (Cohen-Kettenis, 1986).

12.2 Care of Transsexuals 1968–1995

12.2.1 History

In the period after the publication of the above-mentioned books and concurrently with the sexual revolution (1968), the view of "transsexualism" started to change, although slowly. Medical treatment via hormones and "sex reassignment surgery" remained controversial. First, in the 1970s and 1980s psychiatry, certainly in southern Europe, was dominated by the psychoanalytic "discourse," and so was "transsexualism" or "gender dysphoria" (Cohen-Kettenis & Wålinder, 1987). "For human beings, it is as impossible to change sexes as to become a pure spirit and the mutilating operation will only lead into a dead end." This sentence was published in the Summary of a paper written by Caire in 1989 in the "Annales Psychiatriques." Although transsexualism was no longer considered a delusion by most of the Anglo-Saxon professionals, it was still presumed by many to reflect an intrapsychic conflict for which psychotherapy was "the" solution. The aim of this psychotherapeutic approach was to cure the cross-gender identity feelings and to help the person accept his/her sex of birth. Nowadays, this is called "gender reparative therapy" (Byne et al., 2012).

Secondly, evidence for the effectiveness of a medical treatment approach was nearly nonexistent. Only case reports and retrospective studies consisting of small samples were published. A good example is the publication of Wålinder and Thuwe (1975), who concluded, on the basis of the follow-up investigation of 24 sex-reassigned transsexuals, that 2 out of the 11 biological men and none of the biological women regretted the measures that had been taken. Negative predictive factors detected were unstable personality, excessive geographical distance between patient and therapist, and long interruptions of hormone treatment. Even in 2003, a Dutch survey (A Campo, Nijman, Merckelback, & Evers, 2003) demonstrated that most psychiatrists thought that transsexualism was merely an epiphenomenon, a symptom of other psychiatric illnesses, and therapy options proposed to patients depended on their personal view on gender identity disorder. For example, some psychiatrists considered these patients as having a kind of body dysmorphic disorder comparable to anorexia and thus did not need to be treated by surgery.

Third, the world view in those days was still very dichotomized as a woman and a man's world, with little acceptance of diversity. Masculine matched up with man and feminine matched up with woman. As mentioned in the DSM-III, gender identity was seen as the private experience of gender role, and gender role as the public expression of gender identity. All these factors contributed to how transsexualism was conceptualized and the concept was clinically utilized. The diagnosis of "transsexualism" in the DSM-III (the diagnosis "gender identity disorder" for adults was only introduced in 1994 with the fourth edition of the DSM) was therefore rather narrowly defined, with a direct link to therapy. Providing hormonal and surgical sex reassignment surgery was only meant for those persons with extreme gender dysphoria. Clinicians, also influenced by public opinion, were scared to do harm to their patients and were very careful regarding hormonal and surgical sex reassignment therapy. Services were often denied if someone was not considered a "true" transsexual (being the person who wants to live in the other gender than assigned at birth, with a true conviction that he or she was born in the wrong sex, and wants a complete bodily adaptation to the other sex) because only those individuals were thought to be good candidates for sex reassignment therapy, in order to avoid postoperative regret (Cohen-Kettenis & Pfäfflin, 2010).

12.2.2 Diagnosis: Clinical Features

Before 1995, the DSM-III (1980) and the DSM-III-R (1985) were used to diagnose transsexualism, but more importantly it was the pre-Internet period. Online searches for symptoms were not existent and individuals with gender issues and gender dysphoria sought psycho-medical help in very different ways than they do nowadays. Most individuals had difficulty finding their way to the scarcely existing gender teams (Cohen-Kettenis & Wålinder, 1987) and were often held back by general practitioners, psychiatrists, psychotherapists, or other health professionals. Hormones were often bought under the counter. In the late 1960s and 1970s, some chose to undergo sex reassignment in Casablanca where Dr. Burou, a gynecologist, specialized in performing vaginoplasties (Hage, Karim, & Laub, 2007). No psychological evaluation was needed to receive surgery, as no standards of care for transsexuals existed at that time. However, many individuals suffered in silence and tried to cope with their cross-gender feelings without coming out at all.

Individuals who were able to find and contact competent mental health professionals for their gender issues could mainly be divided into two categories: those who had decided on sex reassignment therapy and those who just wanted help with their gender issues, with the knowledge that sex reassignment therapy was one of the therapeutic options, but that comfortable accommodation to their cross-gender identity without medical interventions was another option (Bockting, Knudson, & Goldberg, 2006).

Mental health professionals (psychiatrists, psychologists, or social workers with a specific interest in gender issues) working in private or as part of a multidisciplinary team were very cautious in their diagnostic work. Their first goal was to prevent patient regret of the transition, and they took the whole responsibility on their own shoulders for the decision to allow patients to undergo sex reassignment therapy. Because the diagnosis of transsexualism was based on nonobjective criteria and no psychometric instruments were developed to measure gender-dysphoric symptoms, the diagnosis was lengthy in time (mostly 1 year for the observational phase; see below), divided into two phases, and often information was examined by interviewing a third party (Cohen-Kettenis & Gooren, 1999).

12.2.2.1 First Diagnostic Phase

In the first phase, the observational phase, diagnostic criteria of ICD-9 or the DSM-III (APA, 1980) and later on the DSM-III-R (APA, 1987) for transsexualism were checked by means of a clinical interview. In addition to the criteria concerning the wish to belong to the other gender and to change their bodies, one of the criteria of DSM-III was "absence of physical or genetic abnormality," and another "not due to another mental disorder, such as schizophrenia," but both criteria were skipped in the DSM-III-R diagnosis. DSM-III as well as DSM-III-R asked for an enduring gender dysphoria of more than 2 years before the diagnosis could be proposed.

This was a useful criterion for clinicians to determine if a person was eligible for sex reassignment surgery (SRS) or not. Besides the DSM diagnoses, a thorough psychological/psychiatric assessment was performed to evaluate the psychological and social functioning of the applicant, his/her intellectual and emotional coping mechanisms, as well as possible concomitant psychopathology. The first aim of this evaluation was to be sure that the applicant had no major psychiatric problem or personality disorder that was underlying the diagnosis of "transsexualism" and that could impair the outcome of sex reassignment therapy. Second, a differential diagnosis was established to exclude applicants with the following diagnoses from medical treatment: patients with "transvestism"—but these individuals do not have the wish to be rid of their own genitals—or patients with "atypical gender identity disorder," individuals with a disturbed gender identity who only in isolated periods of stress wish to belong to the other sex and to be rid of their own genitals, or individuals who only seek a partial sex reassignment. Another third aim was to evaluate the already documented negative prognostic factors for postoperative failure (Wålinder, Lundström, & Thuwe, 1978), including psychiatric comorbidity, poor support of the applicant's family, dissatisfaction with secondary characteristics at initial assessment, and inadequate social functioning.

12.2.2.2 Second Diagnostic Phase

The second diagnostic phase is meant to evaluate the applicant during the "real-life test"; this is the period during which the clinician asks the applicant to live permanently in the desired gender role, a requirement mentioned for the first time in the first version of the Standards of Care (Cohen-Kettenis & Gooren, 1999). The applicant can experiment by experiencing "in vivo" how to live in the other gender and by coping with the consequences of this change. In this period, the applicant discloses his gender dysphoria and wish for transitioning to family, friends, and work. A new name is chosen. The aim of this test is also to check if, by living in the opposite gender role, the gender dysphoria will disappear, and thus the need for gender role change. Most clinicians and gender identity clinics in the 1970s and 1980s were expected to request this "real-life test" without hormones. Only after approximately 2 years, when the patient persisted in his/her transgender wish and was happy with the results of the hormonal treatment, he or she was considered ready to undergo surgery.

12.2.2.3 Typology

For clinical purposes, most clinicians recognized a subdivision in types of transsexualism, primary versus secondary transsexualism (in male-to-female transsexuals) (Person & Ovesey, 1974a, 1974b). This classification was made on the basis of the resolution of an ambiguous core gender. Person and Ovesey presumed that primary (true) transsexuals are asexual and have lifelong cross-gender wishes, but do not cross-dress as children and show no fetishistic arousal in adolescence related to their choice of clothing, while secondary transsexuals evolve from effeminate homosexuality or heterosexual transvestitism and experience cross-gender wishes only after puberty. The transsexual wish can follow a stressful period, can be episodic, or can evolve into a long-term identity (Lawrence & Zucker, 2012). These authors, together with others (e.g., Dolan, 1987; Levine & Lothstein, 1981; Meyer, 1982; Stoller, 1968), recommended that all individuals with secondary transsexualism should first undergo psychotherapy (supportive, insight oriented, or a combination of both) before undergoing sex reassignment therapy, to consider their wish for sex change as thoroughly and as objectively as possible (Dolan, 1987).

Blanchard's typology of male-to-female individuals was similar: "homosexual transsexuals" (gender-dysphoric individuals who are sexually attracted to individuals of the same natal sex) and "nonhomosexual transsexuals" (Blanchard, 1985; Blanchard, Clemmensen, & Steiner, 1987). According to Blanchard, the etiology of these categories is different. Nonhomosexual transsexuals experience autogynephilia (Blanchard, 1989), the male's proneness to be sexually aroused by thoughts or images of themselves as women, which can be considered a paraphilia. These individuals were assumed to seek SRS to actualize their autogynephilic desires. In this group, more postoperative regret was noticed (Blanchard, Steiner, Clemmensen, & Dickey, 1989; Lundström, Pauly, & Wålinder, 1984), as these individuals tried to live longer in the male gender role, sought sex reassignment later in life, and dealt with more loss (marriage, family, work) when transitioning. Therefore, clinicians emphasized an extra evaluation during the second phase of the diagnosis. More recent outcome studies though have not found more regret in these individuals with late-onset gender dysphoria, but rather found that they have more difficulties with social acceptance in the new role after transitioning (Lawrence, 2003).

Female applicants were (and still are) considered a more homogeneous group, with most sexually orientated towards women, searching for therapy at a younger age, having fewer psychological disturbances or postoperative regrets (Dolan, 1987; Levine & Lothstein, 1981).

12.2.3 Therapy

Therapeutic options for individuals with gender dysphoria were and remain diverse: psychotherapy (individual therapy, marital or family therapy, or group therapy), hormonal therapy, social transition into the desired gender role, and/or sex reassignment surgery.

In the 1970s and 1980s there was the conviction among professionals that gender-dysphoric persons, with the exception of the "true" transsexual, were probably more accurately treated by psychotherapy. The purpose of this psychotherapy was to improve the understanding of gender issues, to try to cope with them, and to search for alternative solutions to gender problems (Cohen-Kettenis & Gooren, 1999), such as part-time transitioning. In those days, numerous published papers reported successful outcomes of treating adolescents or adults by psychotherapy alone (Barlow, Abel, & Blanchard, 1979; Barlow, Reynolds, & Agras, 1973; Davenport & Harrison, 1977; Kirkpatrick & Friedmann, 1976; Lothstein, 1980). These papers were about psychodynamic and behavioral psychotherapy with the aim of accepting the natal sex and preventing social and physical transition to "the other sex." But conclusions from these (mostly) case studies were difficult to draw: Who were these gender-dysphoric individuals, did they suffer from one of the less severe forms of gender dysphoria, what were the criteria of a successful outcome, was the outcome long-lasting, and was a successful outcome (renouncing SRS) due to therapy or an effect of other determinants (Cohen-Kettenis & Kuiper, 1984; Cohen-Kettenis & Wålinder, 1987)?

For those who were eligible for SRS, supportive psychotherapy, not having the purpose to "cure" the gender dysphoria but to explore the evolving gender identity and the anxieties and ambivalences, to help with "coming out," and to cope with the losses a transition encompasses, was strongly encouraged. These sessions started in the diagnostic phases and continued while the patients were taking hormones in preparation for decisions about surgery. This psychotherapy was mostly individual, but patients could also benefit from group therapy (Stermac, Blanchard, Clemmensen, & Dickey, 1991), reducing the feelings of isolation, providing support in exploring their gender issues, and even providing practical advice on clothing, makeup, and other aspects of gender presentation. Marital or family therapy could help in the resolution of conflicts between spouses or between family members. It was well known from the literature examining prognostic factors for successful SRS that good family support was very important for a positive outcome. From that moment on, some mental health professionals involved the loved ones (partners, parents, children, other family member, etc.) in the counseling of the gender-dysphoric patient.

12.2.4 Standards of Care (SOC): Versions 1, 2, 3, and 4

The World Professional Association for Transgender Health (WPATH), formerly (from 1979 until 2007) called the Harry Benjamin International Gender Dysphoria Association (HBIGDA), is a multidisciplinary professional association devoted to the understanding and treatment of gender identity disorder. In 1979, for the first time, HBIGDA presented an explicit statement on the appropriate standards of care for hormonal and surgical sex reassignment (Walker et al., 1979). Being endorsed by an identifiable professional group, this original statement on the standards of care was expected to provide more clinical guidelines for professionals and improve the care for gender-dysphoric patients. It was recommended that professionals involved in the management of sex reassignment cases use these standards as the minimal criteria for the evaluation of their work. A quote in the introduction of this document demonstrated that carefulness and cautiousness were of primary concern:

> "*It should be noted that some experts on gender identity recommend that the time parameters listed in these standards should be doubled, or tripled* (p. 2)".

These standards were revised by the same members of the founding committee of the HBIGDA in 1980 (version 2), in 1981 (version 3), and in 1990 (version 4) always chaired by Dr. Paul Walker (Walker et al., 1980, 1981, 1990). The different versions all contained 32 principles and 16 standards but were adapted in a slightly more liberal way across each revision. In the first version, the Standards of Care recommended that the applicant eligible for sex reassignment treatment meet the DSM-III criteria of transsexualism (category 302.5x). Preceding the hormonal therapy, the patient should live for 3 months full-time in the social role of the desired gender and should have a psychotherapeutic interaction of a minimum of 3 months with the psychologist or psychiatrist making the recommendation in favor of treatment. For genital surgery, the requirements were professional relationship for at least 6 months with a psychologist or psychiatrist and full-time living in the desired gender for 12 months. Hormonal sex reassignment should precede SRS. Two different clinical behavioral scientists must give their approval for genital surgery. Instead of being considered a counselor, the behavioral scientist held more of a gatekeeper's role, controlling who was eligible for sex reassignment therapy and who was not, without sharing the responsibility of the decision for medical therapy with the patient.

Already in version 2, the requirement that the patient had to live successfully in the desired gender role at least 3 months prior to the hormonal treatment was rescinded. In version 3, the requirement that one of the clinical behavioral scientists giving the written recommendation for genital surgery be a psychiatrist was eliminated. Minimal documentable credentials and expertise of the clinical behavioral scientists who could give written approval for sex reassignment therapy were adopted in version 4.

Most gender identity clinics, as well as private practitioners treating gender-dysphoric individuals in Europe and North America, adhered to the SOC (Petersen & Dickey, 1995). Although these standards, seen through the eye of the professional in 2012, patronized the individual with gender dysphoria, they were also a big step forward in the appropriate care for these patients, preventing them from maltreatment or from being a victim of abuse and unethical practices.

12.3 Care of Individuals with the Diagnosis of Gender Identity Disorder: 1995–2010

12.3.1 History: Terminology

With the introduction of DSM-IV (APA, 1994) and DSM-IV TR (APA, 2000), the diagnosis of transsexualism disappeared and the diagnostic label changed to Gender Identity Disorder. After 1995, more and more papers about GID were published with mainly two foci: follow-up studies of larger cohorts of individuals who underwent sex reassignment therapy and a second focus on etiological issues, with emphasis on the biological brain aspects (e.g., Garcia-Falgueras & Swaab, 2008; Hare et al., 2009; Zhou, Hofman, Gooren, & Swaab, 1995). These papers provided more insight into what gender identity is and presented more evidence for the effectiveness of the medical treatment of gender identity disorder in adults (Byne et al., 2012).

The 1995–2010 period involved the development of the Internet and social networking. Transgender people started to connect with each other in ways that were previously not possible. Consumer organizations emerged and influenced professionals about how to conceptualize, to diagnose, and to treat gender dysphoria. They also influenced the terminology. The term male transsexual was first replaced by male-to-female transsexual and afterwards by trans-woman, and a female transsexual became first a female-to-male transsexual person and afterwards a trans-man. Sexual orientation is now more frequently defined by gender identity and not by natal sex; the terms gynephilic or androphilic became more common. The name "real-life test" was changed into "real-life experience" and is, since the launch of the SOC—version 7, replaced by the paraphrase "living in a gender role that is congruent with the gender identity."

After 1995, more attention was also paid to individuals who do not wish to undergo genital surgery for diverse reasons such as keeping their fertility, or sexual reasons, as well for those who do not want to or cannot transition. Hormonal therapy only, without any surgery, became more acceptable.

12.3.2 Diagnostics

12.3.2.1 Diagnostic Criteria

From 1994 on, the applicant for sex reassignment had to fulfill the diagnosis "Gender Identity Disorder" (GID) according the DSM-IV criteria (APA, 1994) or DSM-IV-TR (APA, 2000) (same criteria). In the GID diagnosis, the same two components as in the earlier versions were present: (a) There is a strong and persistent cross-gender identification, which is the desire to be, or the insistence that one is of the other sex (not merely a desire for any perceived cultural advantages of being the other sex); (b) there must be evidence of persistent discomfort about one's assigned sex or a sense of inappropriateness in the gender role of that sex. Also in the DSM-IV and the DSM-IV-TR manual, the diagnosis cannot be concurrent with a physical intersex condition (criterion c), those individuals with an intersex condition with gender dysphoria are coded GID Not Otherwise Specified (NOS), and to the diagnosis requires evidence of clinically significant distress or impairment in social, occupational, or other important areas of functioning (criterion d) (APA, 1994, 2000). In contrast with the DSM-III diagnosis, the criterion "a strong and persistent cross-gender identification" does not mention any duration of the symptoms in the DSM-IV diagnosis, which gives the clinicians less guidance regarding medical therapy, but gives them more freedom in their interpretation of who is eligible for SRS (Cohen-Kettenis & Gooren, 1999). In DSM-IV and DSM-IV-TR (already in DSM-III-R), comorbidity (such as schizophrenia) is no longer an exclusion as such. The following specifiers may be noted based on the individual's sexual orientation, namely, sexually attracted to males, to females, to both, or to neither. For clinical reasons though, the subdivision made on the basis of sexual orientation, as well as the subdivision in primary and secondary transsexualism, has been abandoned and replaced by the categories early onset versus late onset, which has turned out to be more useful and pragmatic. This subdivision, although not used in the DSM-IV or DSM-IV-TR, is made based on the onset of gender dysphoria. Individuals with early onset have a history of lifelong gender-dysphoric feelings and fulfill retrospectively the diagnosis of GID in childhood; individuals with late onset had no GID in childhood and start having gender-dysphoric feelings later in life, after puberty. Besides the clinical reasons, this subdivision is less stigmatizing and considered more useful for future research purposes (Doorn, Gooren, & Verschoor, 1994; Nieder et al., 2011).

A new phenomenon that has to be considered as a differential diagnostic category, in addition to those already mentioned, is the recently described phenomenon of the "Modern Eunuch." These are men who voluntarily want to be castrated (chemically or physically). The majority identify as male or view themselves as in an alternate non-male, non-female, gender space. Only very few identify as male-to-female transsexuals. Johnson, Brett, Roberts, and Wassersug (2007) suggest that male-to-eunuch is a valid transgender identity. This category is still a clinical description without a formal diagnosis and without well-established therapy.

12.3.2.2 Assessment

To assess more objectively the degree of gender dysphoria, existing gender-related subscales of well-known questionnaires (MMPI-2, Minnesota Multiphasic Personality Inventory-2, Gómez-Gil et al., 2008) were more frequently used, and new scales evaluating gender-dysphoric symptoms were developed. The Utrecht Gender Dysphoria Scale (Cohen-Kettenis & van Goozen, 1997) has been widely used for clinical and research purposes and has now been validated (Kreukels et al., 2012; Steensma et al., 2013). Deogracias developed a Gender Identity/Gender Dysphoria Questionnaire for Adolescents and Adults (Deogracias et al., 2007) with good sensitivity and specificity, which also has been cross-validated (Singh et al., 2010).

The diagnostic phase is performed as in former years (evaluation of the gender dysphoria as well as a thorough psychological evaluation) but with other priorities and foci and a less lengthy time frame (depending on the individual case, sometimes a few evaluation sessions are sufficient). Mental health professionals have become more acquainted with Gender Identity Disorders and gender incongruence and are more guided and backed by outcome studies supporting the effectiveness of sex reassignment surgery. Consumer organizations pushed hard to reduce the time required before hormonal treatment could start, as well as the period of real-life experience, because they considered these diagnostic procedures as needlessly lengthy, stressful, and expensive (Cohen-Kettenis & Gooren, 1999). In an evaluation of more than 200 postoperative MtF individuals, Lawrence (2003) reached the conclusion that the duration of preoperative real-life experience in the desired gender role showed a significant association with "happiness with result" but not with any other outcome measures. In general, in most gender identity clinics, the real-life experience has mostly lost its value as a diagnostic guide and is no longer a requirement for hormonal treatment (see SOC version 7). Living in the preferred/experienced gender could begin even after the hormonal treatment has started. Although requested for genital surgery, the real-life experience was mostly reduced to 1 year before surgery was authorized.

The task of the mental health professional has evolved in fundamental ways. The gatekeeper's role became obsolete, and a working alliance with the patient based on trust and respect became essential. The diagnosis shifted to an evaluation. During these evaluation sessions, the mental health professional together with the patient is expected to discuss all the relevant (gender) issues, the consequences, and the planning of care, in an atmosphere wherein the responsibilities are shared and the decisions are made collaboratively (Pfäfflin, 2007). Sometimes, there is a lack of confidence between the mental health professional and the patient and the work alliance remains strained. In these cases, a separation between assessment and psychotherapy is advised (Bockting et al., 2006).

12.3.3 Therapy

From the 1990s onwards, in contrast with the former period, therapy and, more specifically, psychotherapy for gender-dysphoric individuals became more pragmatic and symptom-based. The etiological vision on the origin of transsexualism (be it somatic and/or psychosocial) is not relevant anymore in the therapeutic approach towards the patient. Patients with early-onset GID or with late-onset GID are receiving the same sex reassignment treatment, if they so wish. Hormonal therapy and sex reassignment surgery is accepted as the best available treatment for individuals with gender dysphoria. The focus of the therapy has become the present distress and its alleviation. Gender reparative therapy has been largely abandoned and is typically judged as unethical (Coleman et al., 2011).

This is also the decade that mental health professionals became more convinced that not all individuals with gender dysphoria need both hormones and surgery to alleviate their gender dysphoria, but that some need only one or neither of these treatment options. Gender transition is nowadays considered to encompass separate social and bodily transitions; not all individuals want both. More individualized treatment has become the rule (Coleman et al., 2011).

In their psychotherapeutic approach, most clinicians and mental health professionals have two parallel foci: first is the gender-related care and second is the care for (if present) other mental health problems. During the general counseling sessions, diverse gender-related issues and concerns can be addressed depending on the individual's needs such as body image (masculinity–femininity), implications of the process of coming out, grief and loss, sexual concerns, fertility concerns, social isolation, spiritual concerns, and violence and abuse (Bockting et al., 2006). As gender identity problems, untreated gender dysphoria, and above all social stigma causing minority stress affect the mental health and the psychosocial functioning of the transgender individual, sometimes more focused care is needed. By treating solely the gender dysphoria, the mental health problems are not always solved (through counseling, hormones, and/or social transition). In other more complex cases with more comorbidity, a specific treatment is needed, for example, by pharmacotherapy in the case of major depression, anxiety disorder, or concomitant psychosis or by more specific psychotherapy (in individuals with eating disorders and/or personality disorders). Sometimes the clinician has to refer his patient to a more specialized clinician or psychiatrist for the treatment of comorbid mental health concerns.

Not all individuals want and need a mental health professional to guide them in the gender transition and ask only for an assessment to get approval for hormones and surgery. They consider that by interacting with a mental health professional, they could be stigmatized. It is well emphasized in the sixth version of the SOC of WPATH though that the present inclusion of GID as a mental disorder in the DSM-IV-TR is not a license for stigmatization. Anyway, in the turmoil of a gender transition, moments of reflection together with a mental health professional can always be beneficial. All versions of the SOC strongly support psychotherapy throughout the transition. On the other hand, the mental health professional enables the gender-dysphoric individual to have access to care and can be helpful in achieving health insurance coverage (Pfäfflin, 2007).

In fact, methodologically well-grounded research to evaluate the requirements for sex reassignment surgery that support better outcomes (better psychosocial functioning and less regret) is still not available. Pfäfflin and Junge (1998) published a 30-year review of follow-up studies between 1961 and 1991, and more than 15 years later Gijs and Brewaeys (2007) stated that there is no scientific consensus about how long the contact with the treatment center, real-life experience, hormonal treatment, and counseling ought to last in order to obtain the best results (De Cuypere & Vercruysse, 2009). Nevertheless, a predictor that has been found to be important for a successful SRS outcome is the criterion described as "an adequate understanding of what surgery can and cannot do." This means that individuals who want to undergo sex reassignment surgery must have a realistic view about what can be achieved through surgical interventions, because surgery removes or damages "healthy" organs irreversibly (Rächlin, 1999). In this light, information sessions during counseling are very useful. The gender-dysphoric individual should have the knowledge of different surgical possibilities, their results, and their implications, including reproductive (im)possibilities, complications, postsurgical rehabilitation requirements, and costs, a requirement that has been addressed in different versions of the SOC since version 5.

Although it is well known that lifelong hormonal treatment guided by an endocrinologist or hormone-prescribing physician is needed and that follow-up by the surgeon is associated with good surgical outcomes, less is known about postoperative follow-up by mental health professionals. Only Rehman, Lazer, Benet, Schaeffer, and Melman (1999) especially stressed the need for additional postoperative psychotherapy, an advice that has been inserted in the SOC version 7.

Recently, the Board of Trustees (BOT) of the American Psychiatric Association (APA) approved the report of the Task Force on Treatment of Gender Identity Disorder (Byne et al., 2012). The primary aim of this report was to answer the question as to whether or not there is sufficient credible literature to support development by the APA of treatment recommendations for GID. With subjective improvement as the primary outcome measure, the current evidence base combined with clinical consensus was judged sufficient to support recommendations for adults in the form of an evidence-based APA Practice Guideline. While other guidelines, policy statements, and Standards of Care exist and are available for mental health professionals in providing care to individuals with GID, the report identified several reasons that recommendations specifically targeted to psychiatrists would be desirable. This could likely have a positive impact on the number of psychiatrists willing to help transgender patients. The report also recommends that additional steps pertaining to gender variance (individuals with any degree of cross-gender identification) be taken by the APA beyond drafting treatment recommendations for GID. These include issuing a policy statement to clarify the APA's position regarding the medical necessity of treatments for GID, the ethical bounds of treatments for minors with GID or gender variance, and the rights of persons of any age who are gender variant, transgender, or transsexual (Byne et al., 2012). This report calls for a variety of measures that would greatly benefit the transgender patients and is therefore well accepted. However, the APA did not reach consensus regarding the question of whether or not persistent cross-gender identification sufficient to motivate an individual to seek SRS, per se, is a form of psychopathology in the absence of clinically significant distress or impairment.

12.3.4 More Recent Versions of the SOC: Versions 5 and 6

12.3.4.1 SOC Version 5: 1998

In 1998 version 5 of the SOC was issued, composed by other committee members than the four editions before, and chaired by Dr. Stephen Levine (Levine et al., 1998). SOC 5 differed significantly from the former editions, not only by its length (33 pages instead of 10) but also by the rather detailed guidelines, with specific attention to subgroups. In this version, as well as in version 6, Gender Identity Disorder is still considered a mental disorder.

The "triadic therapeutic sequence" is a new concept in these SOC, and it works to standardize the medical treatment. If the GID diagnosis according to the DSM-IV is made and the patient meets the requirements for medical therapy, the triadic therapeutic sequence of cross-gender living, administration of cross-sex hormones, and genital (and other) surgeries as medical treatment is put forward. Psychotherapy is not a requirement for the triadic therapy. According to version 5 of the SOC,

> The Mental Health Professional who recommends hormonal and surgical therapy shares the legal and ethical responsibility for that decision with the physician who undertakes the treatment.

In this version of the SOC, the issue concerning the patient's legal and ethical responsibility in the decision for SRS is not addressed.

The SOC—fifth edition distinguishes between eligibility and readiness criteria for hormonal therapy and surgery. These eligibility criteria are set out in the section "Requirements for Hormone Therapy for Adults" and "Requirements for Genital Reconstructive and Breast Surgery." The eligibility criteria are those specified criteria that must be documented before moving to a next step in a triadic therapeutic sequence. Without first meeting eligibility requirements, the patient and the therapist should not request hormones or surgery. The readiness criteria are fulfilled if there is further consolidation of the evolving gender identity and if the patient has made progress in mastering interpersonal issues or in dealing with work and family leading to improving or continuing stable mental health. These readiness criteria are rather subjective and rest upon the clinician's judgment. This sometimes can compromise the relationship between the counselor and patient.

For the first time in the history of care for individuals with gender dysphoria, in this edition there is also attention to adolescents with gender dysphoria. The possibility of treating them with puberty blockers is discussed, and guidelines are given.

In complement to the focus on hormonal treatment and genital and breast surgery, there are also paragraphs on the tasks and training of mental health professionals, on psychotherapy (where emphasis is placed on the benefit of psychotherapy, although not an absolute requirement), and on the real-life experience.

In comparison with the previous versions of the SOC, version 5 gives much more guidance to caregivers but is still mainly focused on the prerequisites that patients need to fulfill.

12.3.4.2 SOC Version 6: 2001

Three years after SOC version 5, a next version was issued and chaired by Walter Meyer (Meyer et al., 2001) and included new Committee Members, except Peggy Cohen-Kettenis and Eli Coleman who were already involved in the fifth version of the SOC. These standards were nearly identical to the former version, but with more nuances and some other highlights.

The therapeutic triadic sequence, according to this version, can be handled in a flexible way and is not necessarily in the sequence of real-life experience → hormones → surgery but could also be hormones → real-life experience → surgery or for biologic females, hormones → breast surgery → real-life experience. This version emphasizes that the complete therapeutic triad of the diagnosis of GID is only one of the variety of therapeutic options and that not all persons with GID need or want all three elements of triadic therapy. The SOC advocate that hormones can also be given to those who do not want surgery or a real-life experience and that hormone therapy alone may provide sufficient symptomatic relief to obviate the need for cross living or surgery.

In this version of the SOC, there is a paragraph added concerning the reproductive needs and rights of persons after a sex transition, reflecting a more public debate. The standards encourage patients to consider and discuss fertility issues prior to starting hormonal treatment. Hormonal therapy leads to decreased spermatogenesis (production of spermatozoa) and eventually to azoospermia (absence of sperm in semen) in trans-women (Wierckx et al., 2012).

Also, more attention has been given to the hormone therapy and medical care for incarcerated persons, advising that housing for transgendered prisoners should take into account their transition status and their personal safety.

Although, at first sight, there are no major differences with the former version of the SOC, this version already put more emphasis on the individual needs of the person with gender dysphoria to engage, for example, in a partial transition and on the human rights every single person with gender dysphoria has, young or old, free or incarcerated, with reproductive wishes or not.

12.4 Care of Persons with Gender Dysphoria from 2010 Onwards

12.4.1 SOC, Seventh Version, 2011

The ambition of the newly revised seventh version of the SOC, named as "Standards of Care for the Health of Transsexual, Transgender, and Gender Nonconforming People," issued during the WPATH symposium in Atlanta 2011, was huge (Coleman et al., 2011). In the new spirit of de-psychopathologization of gender variance since the first decade of 2000 and in contrast with the former versions, this version of the SOC includes a statement concerning gender nonconformity, namely, "Gender nonconformity *should not be judged as inherently pathological or negative, yet gender dysphoria is a specific distress that can be alleviated through medically necessary treatment*." Concerning the question if "gender dysphoria" is a mental disorder or not, the seventh version of the SOC is rather diplomatic and uses the following wording: *"Some people experience gender dysphoria at such a level that the distress meets criteria for a formal diagnosis that might be classified as a mental disorder."*

The new SOC wanted to be more evidence-based and succeeded, for the first time, to cite a lot of background, review, and research literature providing as much evidence as possible for these standards. The clinical guidelines are very detailed (from pages 33–122) and extend beyond providing hormones and surgery. They are about achieving overall health, well-being, and self-fulfillment. These standards have been revised by an International Advisory group of individuals who identify as transsexual and/or transgender to address critiques from former issues of the SOC, which were criticized for creating barriers to care by imposing strict criteria for therapy.

Although the general purpose and use of the standards of care roughly remain the same as in previous editions, to provide safe and effective pathways to achieving lasting personal comfort with the gendered selves of our patients, the tone of the new standards is rather different. The emphasis is on what professionals need to do, rather than what the client needs to do, to have the best suitable therapy. These standards are very flexible and recognize the uniqueness of each patient. There are also several new sections such as E-therapy, Voice and Communication, and considerations for persons with DSD. In this version, the concept of the therapeutic triadic sequence is left behind.

Briefly, the changes are as follows. There is no longer a distinction between eligibility and readiness criteria; these are mostly merged under the criterion: “If significant medical or mental health concerns are present, they must be reasonably well controlled.” Concerning the requirements for hormonal therapy, the same criteria are handled, except that the criterion of real-life experience or psychotherapy for a minimum of 3 months is deleted. The requirements for breast surgery in trans-men remain the same; in trans-women the 18 months of female hormones are no longer a prerequisite to undergo breast surgery; the SOC only strongly recommend taking female hormones for at least 12 months prior to breast augmentation, to maximize breast growth and in order to obtain better esthetic results. Concerning the criteria for genital surgery, 12 months of hormone therapy is still required. Another requirement is “12 months of living in a gender role that is congruent with the gender identity,” but this is no longer mandatory when only gonadectomy (surgical removal of ovaries or testes) is performed. Trans-women, for example, can undergo oophorectomy (removal of ovaries) without having lived in the male role for 12 months. The other prerequisites remain the same, but are worded in slightly different ways.

12.4.2 De-psychopathologization: DSM-5 and ICD-11

The diagnostic labeling of gender-variant individuals with a mental illness by using the diagnosis Gender Identity Disorder became a topic of growing controversy in consumer, professional, and human rights organizations (Lev, 2006). The debate as to whether or not a diagnosis of gender identity disorder is valid, needed, or wanted for adult gender-dysphoric individuals can be considered fundamental, as the new DSM-5 is going to be published in 2013 and the ICD-11 in 2015. One of the major arguments put forth by consumer groups for removal of the diagnosis in the DSM-5 is that gender variance is not, in and of itself, pathological and that having a cross-gender or transgender identity does not constitute a psychiatric disorder (Knudson, De Cuypere, & Bockting, 2010). Classifying gender variance as such perpetuates stigma attached to gender nonconformity. Some authors even mention a stigma-sickness slope. The daily experience of stigma, prejudice, discrimination, harassment, and abuse commonly drives trans-people to the social, economic, and legal margins of society, impacts on their mental and physical health, and edges many of them into situations and patterns of behavior that leave them vulnerable to HIV infection and AIDS-related illnesses (Winter, 2012a). Meanwhile, in 2010, WPATH released a statement urging the de-psychopathologization of gender variance worldwide:

> …The expression of gender characteristics, including identities, that are not stereotypically associated with one's assigned sex at birth is a common and culturally-diverse human phenomenon which should not be judged as inherently pathological or negative. The psychopathologisation of gender characteristics and identities reinforces or can prompt stigma, making prejudice and discrimination more likely, rendering transgender and transsexual people more vulnerable to social and legal marginalization and exclusion, and increasing risks to mental and physical well-being. WPATH urges governmental and medical professional organizations to review their policies and practices to eliminate stigma toward gender-variant people.

The DSM-5 Workgroup on Sexual and Gender Identity Disorders of the American Psychiatric Association received a lot of input from professionals and consumers regarding their work in the revision of the diagnosis of Gender Identity Disorder, including recommendations from WPATH (De Cuypere, Knudson, & Bockting, 2010, 2011). In the discussion concerning the pros and the cons of retaining the GID in DSM-5, the workgroup decided to retain the diagnosis, but to replace the name of the diagnosis by Gender Dysphoria, which implies that the identity is no longer considered disordered, but that a diagnosis is needed for those transgender individuals who, at some point in their lives, experience clinically significant distress associated with their gender variance. Greater access to care was one of the major arguments to maintain a diagnosis of gender dysphoria in the DSM-5.

Whether ICD-11 should have a diagnosis of gender dysphoria is another discussion, since ICD is not a manual of mental disorders but a "classification of diseases and related health problems" with a chapter on "Mental and Behavioural [sic] Disorders." At this moment transsexualism and dual-role transvestism are still categorized in this chapter. The provisional proposal from the Working Group on Sexual Disorders and Sexual Health is to remove the diagnoses from Chap. 5 and to place it in a separate chapter under a new name: Gender Incongruence (Winter, 2012b).

It is obvious from the already published SOC version 7, the new proposals for DSM-5 and ICD-11, that in the coming years more efforts will be made by activists, consumers, professionals, and human rights organizations to continue to destigmatize gender variance and gender diversity to prevent individuals with a gender incongruence from being marginalized, stigmatized, and becoming ill. Efforts will also be made to give these individuals easier access worldwide to professional care in their wish for transition, in the way and the extent to which they want it.

12.4.3 Future

The implications of the de-psychopathologization of gender variance, the new SOCs, the more broadly defined diagnosis "Gender dysphoria" in the DSM-5, and the proposed elimination of the diagnosis "transsexualism" from the Mental Disorder chapter in the ICD-11 for the care of the transgender individual can only be predicted from what is already known at this moment. The intention of these changes is that transgender individuals will feel more respected, less stigmatized, and less imprisoned in the dichotomy of man–woman. There may be more respect for different therapeutic options that give the transgender individual more opportunity to align their transgender wishes and their reality. As the whole spectrum of gender variance becomes a focus of diagnosis and treatment, more people with gender issues may feel that their issues are addressed. Transgender individuals may get a greater opportunity to make decisions about their own lives, yielding more self-confidence and fewer mental health problems. This is of course only an expert opinion. I doubt that in this new era of more autonomy for the patient, there will be more individuals who regret their therapeutic choice. But as scientists we should evaluate this evolution, making it more evidence-based. Therefore, more follow-up research that is methodologically well grounded is still needed.

12.5 Vignette: Illustration of Different Approaches in Different Time Frames

Michael came to visit the Gender Identity Clinic of the University Hospital in Ghent for the first time in 1993; he was 21 years old. At that time he was hospitalized in the psychiatric department of the hospital for suicidality. He had tried to commit suicide by hanging. During the interview with the psychiatrist, he revealed that he felt depressed because his mother did not allow him to dress himself and to go out as a woman.

Michael is the youngest of a family with four boys. Soon after his birth, it became clear that he had psychomotoric retardation. An etiological diagnosis for this retardation has never been established. The mother and father had opposing views about his education and argued a lot about it. The father had also an alcohol problem. When Michael was 7, the parents split. He blamed his father for having left the family and felt abandoned by him. The mother was overprotective towards Michael during his childhood and adolescence. As a child, Michael showed no feminine behavior, chose neutral play options, and preferred boys as peers. His cross-dressing started at 12, from puberty onwards, and included the purpose of sexual excitement when he experienced himself as a woman. From then on, he periodically wanted to be a woman but also had periods during which he felt like a man. When he cross-dressed at home, there was bullying from his elder brother. When Michael first attended the gender identity clinic, he was a rather shy young man, not very feminine in his appearance, difficult in contact, and very silent. He was not always consistent in his complaints. Sometimes he said he wanted a total social and physical transition, sometimes he said he wanted only a social transition helped by hormones, and no genital surgery. During the consultation with his mother, she commented negatively on her ex-husband in the presence of Michael. Michael admired women and disapproved of men. There was a negative identification with the father. An IQ test revealed that Michael had borderline intellectual functioning (IQ: 70–75).

Our advice after several evaluation sessions was to stimulate him to further explore his feminine identity by giving him the opportunity to live as a woman on the weekends and to live as a man during the week. We made some agreements concerning these cross-dressing sessions with the mother and brother, but were not supportive for female hormonal treatment to begin. We also advised him to follow some more intensive therapeutic sessions to cope more easily with the loss of his father. The rationale for our treatment proposal was as follows: Michael suffers from the loss of his father, there is no consistency in his wish to change sex, and he does not want to go through a full physical transition. Our diagnosis was Gender Identity Disorder of Adolescence or Adulthood Non-transsexual Type (302.85) with parent–child problem and borderline intellectual functioning. According the DSM-III-R, Michael was considered not to be eligible for hormonal therapy.

Fourteen years later, in 2007, Michael attended the gender identity clinic again. He presented himself as Michelle, a good-looking girl, and told us he had continuously lived as a woman for 10 years, but still did not take female hormones. In the meantime, she lived apart from her family, under supervision, but was not able to work. She had no partner. She defined herself as being bisexual. The mother was still a supportive figure for Michelle. During the 14 years we did not have contact, Michelle went through some psychotic episodes (approximately five times), always provoked by stress. Antipsychotic medication had now stabilized her mental illness. It was very important for Michelle to be considered a woman; there were no hesitations about that anymore. She wanted female hormones and breast augmentation, without genital surgery. By taking hormones and having breasts, she would obtain the secondary characteristics of a woman, would suffer less from beard growth, and would feel more like a woman. Primary male organs were not so important for her, she was not disgusted by them, and she was very afraid of sex reassignment surgery.

After four evaluation sessions, the psychiatrist of the gender identity clinic gave approval for hormonal therapy. A clear-cut DSM-IV-TR diagnosis was difficult to make, Gender Identity Disorder or Gender Identity Disorder Not Otherwise Specified, but was not so important for our therapeutic plan, as Michelle's wish was taken at face value. Although she had a low IQ, she had the capacity to make a fully informed decision and to consent for treatment. Michelle was very pleased with this decision: With the growth of her breasts, not having erections anymore, and less hair growth over her body, she nevertheless had a relapse of a psychotic period, but it was very short, and she was quickly under control.

After 18 months of female hormones, the gender team consisting of a psychiatrist, endocrinologist, and surgeon agreed to breast augmentation. There was no doubt about her female gender identity, and we agreed on her request for partial bodily transition. One year later, she enjoys her physical transition and thanked the gender team for agreeing to give her hormonal treatment and breast surgery. She functions well and feels much happier than before.

The most impressive change of vision of the gender team over the years was that we now agreed upon a partial physical transition and that we are convinced this decision is in the best interest of Michelle. Also, the low IQ and the periodic psychotic episodes were not anymore absolute contraindications, but only a focus of attention.

12.6 Discussion and Conclusions

When we review more than 50 years of gender care, we can conclude that the view of care for persons with gender dysphoria has changed tremendously. Before the 1970s, transsexualism was viewed as a symptom of major psychopathology, a psychotic illness that had to be treated by antipsychotics or through an intensive (psychodynamic) psychotherapy, helping the patient to accept his or her sex of birth. From the 1970s onwards, more and more psychiatrists and psychologists became convinced that, in some patients, gender dysphoria was an authentic complaint, best treated by medical treatment (hormones and surgery), and not a delusion. These patients needed to be carefully selected and to follow a rather strict procedure of triadic sequence. Only patients with a lifelong cross-gender identity were considered good candidates for sex reassignment surgery.

At that time, secondary transsexualism still needed to be treated by psychotherapy. Later on, mental health professionals agreed that even individuals with late-onset gender dysphoria could benefit from sex reassignment (treatment). Until the end of the previous century, the role of the mental health professional was the role of a stern evaluator, a firm/tough gatekeeper. Their approach was dichotomous, male–female, without allowing partial treatment. The concept of gender variance or gender nonconformity has only become accepted in the last 10 years. The idea is that only some gender nonconforming people experience gender dysphoria at some point in their lives (Coleman et al., 2011), gender dysphoria referring to the distress caused by a discrepancy between a person's gender identity and that person's sex assigned at birth (and the associated gender role and/or primary and secondary sex characteristics). Treatment is meant to help people with such distress to explore their gender identity and find the gender role and bodily adaptation that fits them. The mental health professional is no longer a gatekeeper. Psychiatrists have a role only in treating those individuals with severe psychiatric morbidity hampering the gender care. More attention has been drawn in recent years to the human rights of gender-variant people; to the effect of stigmatization, discrimination, and victimization; and to ways of preventing these.

Although in many countries and regions of the world gender care succeeded in treating gender-variant and gender-dysphoric individuals with dignity and respect, improving their quality of life, still many individuals do not have access to this high quality of care for diverse reasons, e.g., geographical, financial, social, religious, and familial or other reasons. This will be one of the foci or challenges in the upcoming years. Research on etiology and treatment with the aim of continuously improving the care of gender-dysphoric individuals (taking into account the newer concept of gender dysphoria) remains another focus.

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Chapter 13
Psychiatric Comorbidity in Adults with Gender Identity Problems

Luk Gijs, Ellis van der Putten-Bierman, and Griet De Cuypere

Abstract For many decades of the twentieth century, gender dysphoria was seen as an intrinsic symptom of another psychiatric disorder (e.g., schizophrenia) that should be resolved by addressing the "underlying" psychiatric disorder. DSM-III (American Psychiatric Association, 1980) broke with that view and classified the gender identity disorders as a separate category of psychopathology. In contrast, many argue today that gender nonconformity and even gender dysphoria are not (psycho)pathology per se and that sex reassignment therapies are the most effective therapies for gender dysphoria (e.g., World Professional Association for Transgender Health, 2011).

However, based on the prevalence rate of comorbidity, many are convinced that the diagnosis and treatment of psychiatric comorbidity is of paramount importance for a proper diagnosis and for a successful treatment of gender dysphoria.

This chapter reviews the prevalence rate of comorbid Axis I and II disorders in persons with gender dysphoria (GD), explores theoretical models to explain comorbidity,

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and describes clinical implications. The central message is that we should avoid two pitfalls: First, we should avoid the assumption that all patients with GD must have comorbid disorders, and second, we should not assume that patients with GD will not have comorbid disorders. However, to ensure the best possible outcome of sex reassignment therapy and to prevent regret, comorbidity should be diagnosed and treated properly.

13.1 Introduction

For most of the twentieth century, transsexualism has been conceptualized as a severe symptom of a psychiatric disorder (e.g., schizophrenia, borderline personality disorder, identity disorder) and was treated accordingly (see Chap. 12; e.g., Socarides, 1969, 1970, 1988; Stoller, 1996; Volkan & Greer, 1996). Since 1980, this viewpoint is no longer shared by the Diagnostic and Statistical Manual of Psychiatric Disorders. In that year, DSM-III classified transsexualism as a separate and independent psychiatric disorder (see Chap. 7 for an overview of the nosological classification and terminology). Transsexualism was characterized by "an incongruence between anatomic sex and gender identity" (DSM-III, 1980, p. 261). Although transsexualism was no longer considered to be a symptom per se of another psychiatric disorder, it was assumed in the DSM-III (1980, p. 263; see also p. 265) that psychological factors, and especially a disturbed parent child relationship, were major developmental determinants of transsexualism. Furthermore, DSM-III (1980) stated that many persons with transsexualism experienced anxiety and depression and had in general a "moderate to severe co-existing personality disturbance" (DSM-III, 1980, p. 262). Unfortunately, DSM-III (1980) did not provide information on how the prevalence of comorbidity in adults with gender identity problems was measured and what clinical implications comorbidity has.

Today, transsexualism/transgenderism is, in general, no longer seen as a symptom of psychopathology. The World Professional Association for Transgender Health (2011) expressed, in the 7th edition of the Standards of Care (SOC), the view that

> "*the expression of gender characteristics, including identities, that are not stereotypically associated with one's assigned sex at birth is a common and culturally-diverse human phenomenon [that] should not be judged as inherently pathological or negative*." (SOC 7 2011, p. 4)

It is specified further that

> Gender nonconformity *refers to the extent to which a person's gender identity, role, or expression differs from the cultural norms prescribed for people of a particular sex*. Furthermore,

> "Gender dysphoria *refers to discomfort or distress that is caused by a discrepancy between a person's gender identity and that person's sex assigned at birth (and the associated gender role and/or primary and secondary sex characteristics).*" It was expressed that only

> some *"nonconforming people experience gender dysphoria at* some *point in their lives"* and *"Some people experience gender dysphoria at such a level that the distress meets criteria for a formal diagnosis that might be classified as a mental disorder. Such a diagnosis is not a license for stigmatization or for the deprivation of civil and human rights*" (SOC 7 2011, p. 5).

This is quite a different view than that of most professionals during the twentieth century who considered transgenderism as part of another psychiatric disorder. Gender nonconformity is definitely no longer considered as a psychiatric disorder per se. Although there remain different answers to the question of whether gender identity problems should be classified as a psychiatric disorder (DSM-5 will still classify gender dysphoria as a psychiatric disorder), there seems to be an agreement that sex reassignment therapies are effective and should be tailored to the specific needs of an individual (e.g., Bockting, 2008; Byne et al., 2012; Lev, 2004; Murad et al., 2010; Selvaggi & Bellringer, 2011; but see á Campo, Nijman, Merckelbach, and Evers (2003) for an opposing view). One aspect of good care is, according to the SOC 7, that "other mental health concerns" should be screened, diagnosed, and treated (by psycho- or pharmacotherapy). So, clearly, the SOC 7 recognizes that psychiatric comorbidity is an important topic in treating persons with gender dysphoria. This is not without reason because research showed that comorbidity is rather common in patients. For example, Bockting, Coleman, and Benner (2007) found that 35 % of a transgender population reported anxiety and that 44 % felt depressed. Dhejne et al. (2011) reported that persons with transsexualism have a much higher risk of suicide and suffer from more psychiatric comorbidity than matched controls. The greater suicide risk in transgender populations was also signaled in a recent review by Haas et al. (2011) that revealed the suicide rate among transsexual persons to be much higher than in the general population. Based on the empirical literature, Haas et al. (2011) estimated the prevalence of suicidal deaths in transgender people to be 800 for every 100,000 transsexuals after surgery compared to 11.5 suicides per 100,000 people for the overall US population. Associated factors were depression, anxiety, substance abuse, discrimination, violence, and stigma. Furthermore, these authors concluded that approximately one third of self-identified transgender persons made at least one suicide attempt. It is also important to note that, even in persons with a gender identity disorder and no psychiatric comorbidity, the life rate of suicidal ideation was 72 % in a Japanese sample of 500 persons (Terada et al., 2012). Also, the fact that (severe) psychiatric comorbidity is a predictor of regret after sex reassignment (e.g., Gijs & Brewaeys, 2007; Pfäfflin, 1992) and a worse outcome after sex reassignment therapy (Murad et al., 2010) points to the importance of attention to psychiatric comorbidity in the care of people with gender dysphoria.

These worrisome trends led us to the following questions: How many adults with gender dysphoria have psychiatric comorbidity? What is the nature of that comorbidity? Are there specific processes that cause the associations between psychiatric disorders and gender dysphoria? What are the diagnostic and treatment implications of psychiatric comorbidity? And what are the burdens of psychiatric comorbidity for the clinician treating persons with gender dysphoria? In this chapter, we will focus on the prevalence of the co-occurrence of gender dysphoria and psychiatric disorders, the conceptualization of this co-occurrence, and the diagnostic and therapeutic implications of psychiatric comorbidity in persons with gender dysphoria.

13.2 The Co-occurrence of Gender Dysphoria and Psychiatric Disorders (Prevalence)

It is important to note that different terms are used for the description of the occurrence of (at least two different) psychiatric disorders in one adult: covariation, co-occurrence, and comorbidity (Trull, Scheiderer, & Tomok, 2012). Some prefer one of these three terms and that preference is mostly associated with the idea that the term with the least etiological connotation should be used (see Trull et al., 2012). In this chapter, the terms comorbidity and co-occurrence are used interchangeably and descriptively without implying common etiological paths or determinants. Unless directly relevant for the topic of this chapter, we will not go into methodological aspects of comorbidity research (see Hyman, 2010; Links, Ansari, Fazalullasha, & Shah, 2012; Trull et al., 2012).

13.2.1 Comorbidity on Axis I

The prevalence of comorbid Axis I problems varies greatly across different studies (Heylens et al., 2013; Lawrence, 2007; Lawrence & Zucker, 2012). For example, Cole, O'Boyle, Emory, and Meyer (1997) reported comorbid schizophrenia in 1 % of patients with gender dysphoria, while á Campo (2003) reported schizophrenia in 24 % of patients with gender dysphoria. In contrast, Heylens and colleagues (2013) found that in a large group of 721 patients in four European gender centers, psychotic disorders were rare (1.5 %). Mood and anxiety disorders are probably the most frequent comorbid disorders in patients with GD: Heylens and colleagues (2013) found that 38 % had a co-occurring Axis I disorder. Of those 38, 61 % suffered from an affective disorder and 17 % from an anxiety disorder. Lawrence (2007) and Lawrence and Zucker (2012) concluded in two reviews that comorbidity in adults with gender dysphoria varies between 6 and 80 % on Axis I. Terada et al. (2012) found that of 603 consecutive patients who consulted an academic gender identity clinic, 579 fulfilled the diagnostic criteria for gender identity disorder (GID) and 13.6 % had Axis I comorbidity. Also, Gómez-Gil, Vidal-Hagemeijer and Salamero (2008) found in their Spanish study that most of their patients (75 %) had no significant psychopathology on the MMPI-2 (besides atypical scores on the Masculinity-Femininity Scale). Besides methodological differences between studies, as, for example, differences in measurement of comorbidity, the time point when comorbidity is assessed, differences in inclusion and exclusion criteria for the admission to start the diagnostic process, and different sample sizes, we do not know how to conceptually explain this great variation in comorbidity on Axis I.

How does the prevalence rate of co-occurring Axis I disorders in patients with GD on average compare to the general population? Heylens and colleagues (2013) reported a higher prevalence of Axis I disorders in patients with GD than in the general population mainly due to the high prevalence of affective and anxiety disorders, which are up to three times higher. In the general population, current affective problems are found in 6 % (for Belgium and the Netherlands) and in around 10 % (for Germany and Norway), whereas 27 % of the patients with GID in the four countries had current affective problems (Heylens et al., 2013).

In this multicenter European study, the lifetime prevalence of Axis I disorders was almost 70 % (Heylens et al., 2013). A figure much higher than in many earlier studies: Lawrence and Zucker (2012), for example, reported, in their overview, a lifetime prevalence between 21 and 55 % in people with gender dysphoria. Despite these differences, Lawrence and Zucker (2012) agree with Heylens and coworkers that the lifetime prevalence of comorbid Axis I disorders is higher in patients with GD than in the general population. Heylens et al. (2013) reported that, in the general population, a lifetime prevalence for mental disorders is found in 25 % (in Norway, Germany, the Netherlands, and Belgium, compared to the almost 70 % in their patients with GD). Interestingly, and in clear contrast with some earlier studies (e.g., Smith, van Goozen, Kuiper, & Cohen-Kettenis, 2005b), they did not find a different prevalence of Axis I disorders between different types (early versus late onset; male-to-female versus female-to-male) of patients with GD. This result reminds us that, in recent studies, the satisfaction with sex reassignment surgery was as good for homosexual as for heterosexual transpersons (e.g., Lawrence, 2003; Smith, van Goozen, Kuiper & Cohen-Kettenis, 2005a; Smith et al., 2005b), which was explained by Lawrence (2003) as the result of an improved social tolerance and acceptance of transgenderism and homosexuality than in earlier days.

13.2.2 Comorbidity on Axis II

If one—as in DSM-III (1980)—assumes that persons with gender dysphoria have a disturbed personality, one would predict a higher rate of personality disorders in gender dysphoric persons. Indeed, some studies found elevated rates of personality disorders in transwomen and transmen. For example, Hepp and colleagues (2005) reported a prevalence rate of 42 % of personality disorders in patients with GD, and Madeddu and coworkers (2009) reported an even higher rate of 52 % personality disorders in a sample of 50 patients with GD. More precisely, they found that (of that 52 %) 22 % had a cluster B disorder, 12 % a cluster C disorder, 2 % a cluster A disorder, and 16 % had a not otherwise specified personality disorder. Lawrence (2007) and Lawrence and Zucker (2012) concluded in their reviews that comorbidity on Axis II in adults with gender dysphoria varies in different studies between 20 and 70 %.

If this high prevalence rate would be replicated, the diagnosis and treatment of personality disorders should be a major target in the care of transgender persons. However, there are also studies that reported a low prevalence of personality disorders in patients with GD [e.g., Hoenig and Kenna (1974), 18 %; Haraldsen and Dahl (2000), 20 %]. In the biggest study to date, an even lower prevalence was found in Germany, Norway, and Belgium: ±15, 3 % of the patients with GD had a personality disorder at admission (Heylens et al., 2013). Prevalence rates were not very much higher than the prevalence rate for personality disorders in the general population, which is approximately 10.5–12 % Torgersen, 2012; see also Heylens et al. (2013). If these results are replicated, this will cast further doubt on the idea that persons with gender dysphoria always or very often have a disordered personality.

13.3 Models of Comorbidity

Taking into account the results of the research conducted thus far, there can be little doubt that psychiatric comorbidity is rather common in persons with gender dysphoria. However, it is important to realize when comorbidity was measured, for example, when the gender identity disorder started and when a person consulted a professional for diagnosis and help, during hormonal treatment, before or after sex reassignment surgery, or at follow-up. In the literature, it is often not very clear at what moment comorbidity is exactly measured, but Murad and coworkers (2010) concluded on the basis of 28 studies, with 1,833 transpeople (1,093 transwomen and 801 transmen) and an average follow-up of 6 years, that 78 % of transitioned transpersons showed less psychiatric comorbidity after treatment of gender dysphoria than before. A similar result was found in the earlier outcome studies under the leadership of Cohen-Kettenis (Smith et al., 2005a, 2005b).

How do we understand this comorbidity? Although formal models of comorbidity have been developed (Links et al., 2012), to our knowledge these models have not been systematically applied to the field of gender dysphoria. However, within the field of gender dysphoria, different models explaining the comorbidity of gender dysphoria with other psychiatric disorders have been used. For example, Lawrence and Zucker (2012) gave four explanations: (1) Social stigma as a result of an atypical gender identity leads to the development of other psychiatric disorders, (2) the presence of another psychiatric disorder contributes to the development of gender dysphoria, (3) the comorbidity is the result of biological or social risk factors that makes a person vulnerable for the development of various psychiatric problems, and (4) gender dysphoria causes other psychiatric problems. Here, we will focus on the following models: (1) gender dysphoria as a symptom of another psychiatric disorder (the historical model), (2) comorbidity as the result of common pathways that

Fig. 13.1 Gender dysphoria as a symptom of an underlying or more pervasive psychiatric disorder

makes a person vulnerable to the development of different psychiatric problems (a combination of explanations 1 and 3 of Lawrence and Zucker (2012), in which we view stigma also as a social risk factor), and (3) gender dysphoria leads—if not recognized early and treated properly—to the development of psychiatric comorbidity.

13.3.1 Gender Dysphoria as a Symptom

This model, which has lost most of its followers today, is the model that dominated the professional literature roughly between 1945 and 1970 [see Meyerowitz (2002), for a historical account] and conceptualizes gender dysphoria as a symptom of (severe) underlying psychopathology (see Fig. 13.1). Psychodynamic and behavioral models have been influential models for this notion.

13.3.1.1 Psychoanalytic Models

Psychodynamic models (e.g., Chiland, 2003; Socarides, 1988; Stoller, 1996) view transsexualism as a defense mechanism against unresolved developmental conflicts in early childhood. A well-known representative of this view is Socarides who views transsexualism as the result of a failure of the separation-individuation phase between 6 months and 3 years of age due to the failure to give up the primary identification with the mother. Socarides further conceptualizes the other “perversions” as oedipal, but congruent upon the earlier problems in the individuation-separation phase. In other words, this model predicts that transsexual persons should have more severe psychopathology than persons with other “perversions” and less reality testing and predicts a high comorbidity between the different “perversions.” Some even argued that there was a close connection between transsexualism and schizophrenia, but not all psychoanalysts shared that view [see for reviews Chiland (2003), Socarides (1988) and Stoller (1996)]. Not restricting herself to transwomen, Chiland (2003, p. 162) summarized the general view on the developmental disorder underlying transsexualism quite well:

> “*It seems to me that the driving force in transsexuals of both sexes is the failure to overcome a terrifying primal scene, and that they imagine the penis, to a much greater extent than the vagina, to be dangerous; this compels them either to idealize a feminine image, out of the*

> *reach of the penis, such as the long, swirling dress that represents narcissistic plenitude—an image with to conform (in the case of male-to-female transsexuals)—or to expel every vestige of femininity from themselves with a view to finding it again in a female partner who will have nothing to fear from penetration, which has been ruled out once and for all (in the case of female-to-male transsexuals). In most of the described psychopathological models thus far transsexualism is seen as a symptom of a developmental disorder.*"

A more radical psychopathological view is the perspective that considers transsexualism not as a disruption of the development of a normal gender identity but as a symptom of a psychotic disorder. Volkan and Greer (e.g., 1996), for example, sees the transsexual phenotype as the symptomatology of "an encapsulated infantile psychotic self" (p. 167). This means, according to Volkan and Greer (e.g., 1996), that the core of transsexualism is a defense against the internal representation of a depressed mother, associated with emotions such as sadness, rage, or helplessness, which affects the person so negatively that, in an attempt to cure this "negative mother," the person seeks relief by changing the body.

13.3.1.2 Behavioral Conceptualizations

Conceptualizations from a behavioral therapeutic viewpoint saw transsexualism, just like the other sexual deviations, as the result of an atypical learning history (e.g., Barlow, Reynolds, & Agras, 1973; 1979; Barlow & Abel, 1976; Brownell & Barlow, 1980). Transsexualism was defined as the phenomenon in which a normal biological man or woman thinks, feels, and acts as a person of the other sex. As such, transsexualism was seen as the most severe form of sexual deviancy and as the result of behavioral deficits and excesses. Four dimensions were thought of as crucial for sexual deviance: (1) excessive deviant sexual arousal, (2) inadequate normative sexual arousal, (3) deficits in heterosocial skills, and (4) abnormalities in gender role behaviors. As far as our knowledge goes, in the case of transsexualism, behavior therapists thought that the most salient features of transsexualism were (sometimes) homosexual arousal (which was often not accepted by the person) and gender deviant role behavior. Therapy was directed to normalizing behavior on all four dimensions with the result that transsexualism would disappear. A clinical illustration is given by Andrade, Kumaraiah, Mishra, Chatterji, & Andrade (1995). They treated a 24-year-old male student, who felt that she was a person trapped in a male body. Gender atypical behavior was present since childhood, and the child was treated in the family of origin as a girl and allowed to take up a feminine role. Initially, there was no distress. But from the age of 17, the person wished to have breasts and female genitalia. After learning that it was not possible to become pregnant and give birth, the person agreed to a therapeutic program aimed to cure his transsexualism. After being treated for epileptic seizures, a behavioral program was applied. The program had two aims: (1) to reverse the female role (and in consequence the female identity) and (2) to change the homosexual orientation of the person to a heterosexual one. The therapy consisted of 20 sessions of relaxation training to counter depression and frustration, 20 sessions of electric aversion therapy to reinstall heterosexuality and to extinguish homosexuality, and 40 sessions of a combination of modeling, hypnosis, orgasmic reconditioning, behavioral counseling, and sex education. According to Andrade and coworkers (1995), therapy was successful: The person accepted a male gender identity and role, but retained a homosexual orientation. After a follow-up of 2 years, the male gender identity had not changed.

For approximately 30 years now, behavioral conceptualizations have lost their popularity for explaining transsexualism, and behavioral treatments “to cure” transsexualism are seldomly used in clinical practice (Andrade et al., 1995). Possible reasons for the declining interest in behavioral conceptualizations and treatments are: (1) the view that transsexualism can be cured is no longer held; (2) rather than curing transsexualism, the body should be aligned with the mind to solve gender dysphoria or gender incongruence; (3) there are no outcome data proving that behavior therapy is effective; and (4) in contrast to the earlier behavioral conceptualizations, gender identity problems are no longer seen as disorders of sexual desire, sexual arousal, or sexual orientation.

13.3.2 Comorbidity as the Result of Common Developmental Determinants

In this model, the comorbidity between gender dysphoria and psychiatric disorders is the result of a common set of determinants (compare Cochran & Mays, 2006; Cramer, Waldorp, Han, Van der Maas, & Borsboom, 2010; Hyman, 2010; McLaughlin, Hatzenbuehler, Xuan, & Conron, 2012). However, not all models assume the same common determinants or the same temporal order. We differentiate between a vulnerability model in which risk factors lead to the common but independent development of gender dysphoria and comorbidity, and a model in which vulnerabilities lead to the development of a psychiatric disorder which makes the person vulnerable to the development of gender dysphoria. Of course, it will be no surprise that some models put more weight on biological factors, others on environmental factors, and still others on the interactions between both (Hines, 2011).

13.3.2.1 Gender Dysphoria and Comorbid Psychopathology Are Separate Disorders

The basic idea of this view is that the same risk factors are contributing to the development of gender dysphoria and other psychiatric disorders. For example, some would argue that problematic and inconsistent upbringing by parent figures is a risk factor for the development of both gender identity problems and borderline personality disorder (Neeleman, 2007; compare Singh, McMain, & Zucker, 2011),

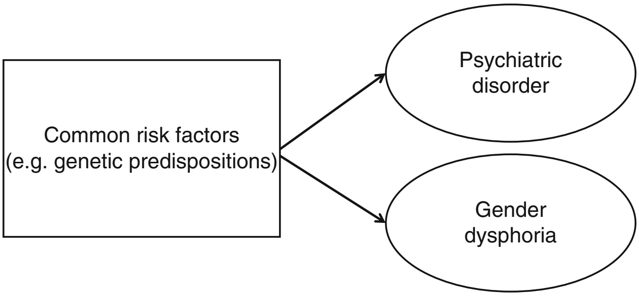

Fig. 13.2 The same risk factors lead to comorbidity between gender dysphoria and psychiatric disorders

two conditions in which identity problems are key symptoms (DSM-IV-TR, American Psychiatric Association, 2000) (see Fig. 13.2).

Other psychosocial variables which are mentioned as risk factors for the development of psychiatric problems are affective neglect, sexual abuse, or attachment problems. However, there is at this moment no solid evidence that this model provides a good explanation for the comorbidity of gender dysphoria and psychiatric disorders. For example, the co-occurrence of borderline personality disorder and gender dysphoria has not always been found. Singh et al. (2011) did not find a single case of GD in a series of 100 females with a diagnosis of borderline personality disorder. But even if comorbidity is strongly and consistently associated, it is not known which factors are responsible for the comorbidity, because prospective longitudinal research on this topic is nonexistent. And of course, besides common psychosocial determinants or pathways, one could also think of common biological pathways (compare Hyman, 2010; South, Reichborn-Kjennerud, Eaton, & Krueger, 2012).

13.3.2.2 Vulnerabilities for Psychiatric Disorders as a Precursor of Gender Dysphoria

Another model is based on the idea that psychiatric disorders and gender dysphoria are linked as a common pathway in the sense that (some) psychiatric disorders are risk factors for the development of gender dysphoria (see Fig. 13.3).

The most influential model of this kind is in all probability Zucker's model of the development of gender identity disorder in children [e.g., Zucker & Bradley, 1995; see also Wallien (2008)]. In Zucker's model, a gender identity disorder in children is thought to be the result of the interaction between general and specific factors. The general factors are twofold: A high level of insecurity or anxiety and sensitivity to parental affect make the child vulnerable for a GID. When there is a familial context (e.g., as a consequence of depression of the mother or intense relational conflicts between the parents) that increases the insecurity and anxiety in the child, the child will try to find a solution for his insecurities and anxieties. One way to

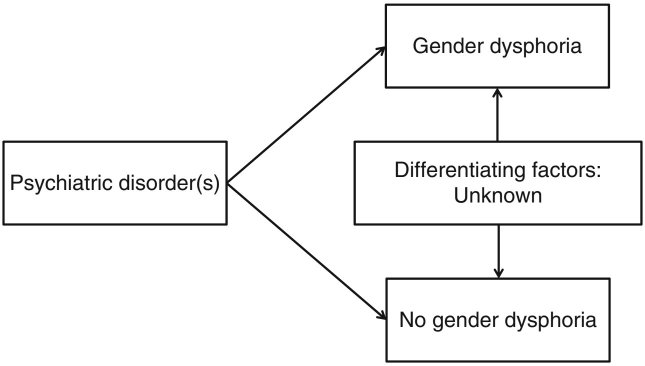

Fig. 13.3 Psychiatric disorder(s) as risk factor(s) or determinant(s) of gender dysphoria

reduce insecurity and anxiety is by adopting a gender identity of the other sex, because that "other gender identity" provides a strong relief from anxiety and insecurity. The reason for this is that in the perception, feelings, and thoughts of the child, the "other gender identity" is more nurtured, valued, and reinforced than the gender identity that is congruent with its natal sex. However, Zucker's model cannot explain why in some children gender dysphoria in childhood will continue into adulthood and in others it will not (see also Chap. 8 by Domenico Di Ceglie on the question "Who becomes a 'desister' or 'a persister'").

Other psychiatric disorders have recently received a lot of attention as vulnerability factors for gender dysphoria, most notably autism spectrum disorders (e.g., De Vries, Noens, Cohen-Kettenis, van Berckelaer-Onnes, & Doreleijers, 2010; Jones et al., 2012; see also Chap. 9), mental retardation (e.g., Parks & Hall, 2006), borderline personality disorder (e.g., Neeleman, 2007; Singh et al., 2011), and psychotic disorders (e.g., Baltieri & De Andrade, 2009; De Cuypere, 1993; Mizock & Fleming, 2011). Two empirical facts hamper the general applicability/validity of these models as general models of comorbidity: (1) Many persons with gender dysphoria do not have a(nother) psychiatric disorder, and (2) many persons with one of the mentioned psychiatric disorders do not have gender dysphoria. So unknown other factors are influencing the development of gender dysphoria.

13.3.2.3 Stress

What about stressors? It is conceivable that stigma, discrimination, oppression of gender variation, and being a victim of (sexual) violence contribute to the development of psychiatric disorders (including gender dysphoria) and their comorbidity. For example, in a recent longitudinal study, McLaughlin and colleagues (2012) found that higher rates of child abuse, housing adversities (i.e., being homeless or being forced out of the home by parents or caregivers), and intimate partner violence contribute significantly to higher rates of psychiatric disorders in LGB

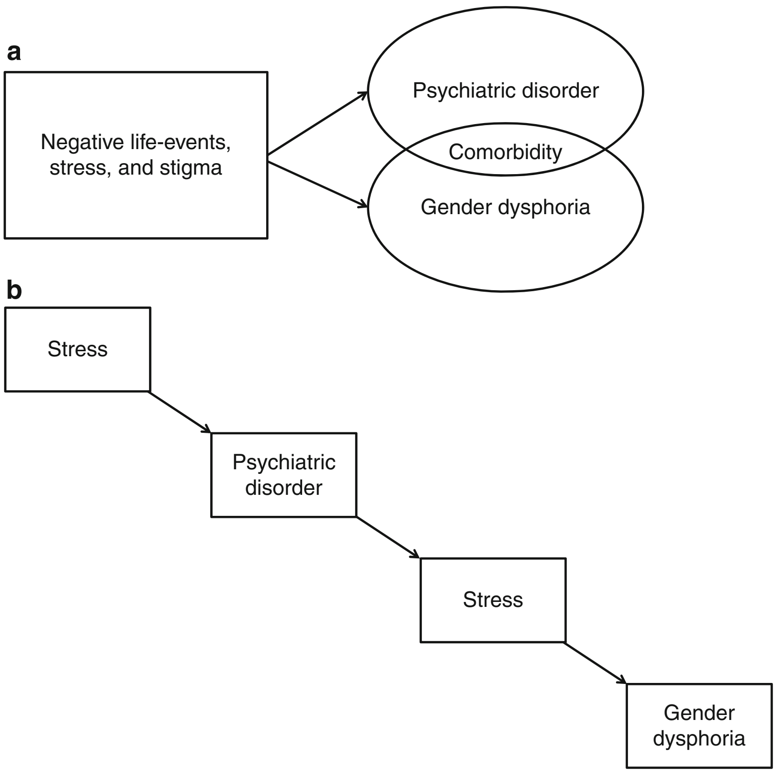

Fig. 13.4 Two models of the influence of negative life events (e.g., violence), stress, and stigma in the development of comorbidity between gender dysphoria and psychiatric disorders: (**a**) Negative life events, stress, and stigma lead to comorbidity; (**b**)Stress leads to a psychiatric disorder, which generates stress and leads to gender dysphoria

(lesbian-gay-bisexual) populations. We know that transgender people are victims of high rates of sexual violence and stigma and oppression (e.g., Nuttbrock et al., 2009). So a model can be built in which comorbidity is (partly) explained by stress, stigma, oppression, and exposure to violence (see Fig. 13.4). In one variant, stress, together with the other variables, causes (or contributes) directly and simultaneously to the co-occurrence of both gender dysphoria and psychiatric disorders (independently). In another variant, stress contributes to the development of psychiatric disorders which in turn lead to the development of further stress and gender dysphoria. Not only can a theoretical model be built which explains the detrimental effects of stress, oppression, and violence, but increasing empirical research validates this viewpoint (see also Chap. 16). With regard to minority stress, we have learned from studies in homosexual and lesbian populations that stress, violence, stigma, and oppression are important determinants of psychological problems (e.g., Lehavot & Simoni, 2011; McLaughlin et al., 2012; Meijer, 2007; Newcomb & Mustanski, 2010). Here, we only give a prototypical illustration (for reviews see

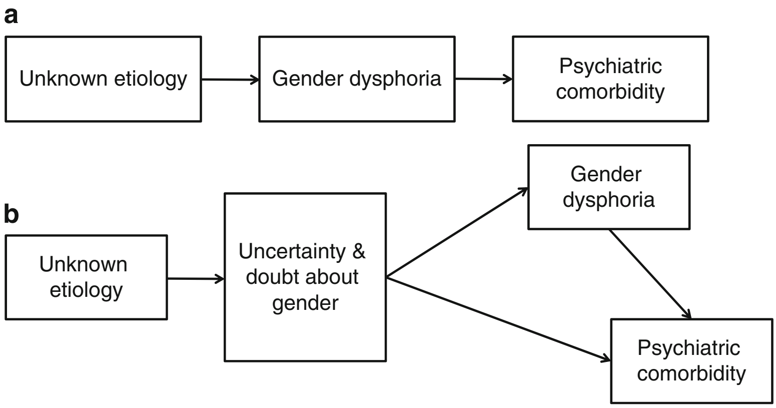

Fig. 13.5 Two models with gender dysphoria as the source of psychiatric comorbidity: (**a**) Gender dysphoria as the source of psychiatric comorbidity; (**b**) Uncertainty about gender and gender dysphoria as sources of comorbidity

Meijer, 2007; Bockting, this book). Nutbbrock and colleagues (2009) used the Life Chart Interview to study how many male-to-female transgender persons were victims of gender-related abuse and what the consequences of such abuse were. They found that no less than 78.1 % reported psychological abuse and 50.1 % had been a victim of physical abuse. In adolescence, most abuse was committed by parents and family members. Among adults, most abuse was perpetrated by strangers, neighbors, friends, and police officers. In general, the prevalence of abuse declined from adolescence to early middle age. The effects of abuse were very clear. In adolescence, abuse strongly contributed to the incidence of depression and suicidality and, in adulthood, the influence of abuse declined for depression but not for suicidality (Nuttbrock et al., 2009).

In our opinion, these empirical data have important implications: Regardless of coexisting psychopathology, stigma, oppression, and exposure to violence contribute negatively to mental health. From a public health perspective, it is important to develop strategies to prevent those negative impacts, and (also clinically) it is necessary to strengthen the resilience and coping strategies of people with gender problems (e.g., Singh, in press).

13.3.3 Gender Dysphoria as the Source of Psychiatric Comorbidity

A last model to consider is that gender dysphoria, especially the distress experienced by persons with gender dysphoria, may be a major source of psychiatric comorbidity (see Fig. 13.5). In other words, if the distress of gender dysphoria persists too long and/or is too intense, psychiatric comorbidity is very likely. Especially in persons with an onset of gender dysphoria later in life (late onset), it may take a long time before persons understand what is going on with them and label themselves as gender variant, transgender, or gender dysphoric. The doubts and uncertainties surrounding this process may also contribute to the development of comorbidity, especially anxiety and affective disorders (Heylens et al., 2013). If it is the case that gender dysphoria itself is a major source of psychiatric comorbidity, it remains to be explained when, how, and to which psychiatric comorbidity gender dysphoria leads. Maybe, in some instances, psychiatric comorbidity is a strategy to protect or facilitate the experience of the desired gender. There are, for example, indications that eating disorders in persons with gender identity disorder are an attempt to bring the body as much as possible in line with the experienced/desired gender (Algars, Alanko, Santttila, & Sandnabba, 2012; Hepp & Milos, 2002). Furthermore, one would expect that finding an understanding of what is going on, giving it a name (e.g., transsexualism/transmen) and reaching a satisfying gender match between "mind and body," would lead to less (or at least less intense) psychiatric comorbidity. The improvement in psychological functioning after sex reassignment surgery is clearly in line with this viewpoint (Murad et al., 2010; Smith et al., 2005a, 2005b). Also in line with this approach is the fact that persons with early onset gender dysphoria have less comorbidity than persons with a late onset (e.g., Smith et al., 2005a, 2005b). However, a different prevalence rate of psychiatric comorbidity for early versus late onset was not found in the multicenter study of Heylens and colleagues (2013).

13.4 Diagnostic and Therapeutic Implications

What are the diagnostic and clinical consequences of the frequent co-occurrence between gender dysphoria and psychiatric disorders and the fact that we do not know what the causal links are between these phenomena? This question will be answered for three different periods around treatment: diagnostics, therapeutics, and aftercare. We want to mention explicitly—and we agree with Levine and Solomon (2010) and with Mizock and Fleming (2011)—that good empirical data about the relations between psychiatric comorbidities and outcome effects are lacking. But this does not free us from the obligation to be explicit about clinical decision making.

13.4.1 Diagnostic Implications

Two different questions need to be answered: (1) When would comorbidity be a contraindication for the start of sex reassignment therapy? (2) When would comorbidity be a signal to discontinue a sex reassignment treatment that is already initiated?

If gender dysphoria covaries solely with the occurrence of a psychiatric disorder with impaired reality testing, most clinicians will argue that it is imperative not to start a sex reassignment therapy, but instead to treat the psychiatric disorder first that is causing the gender dysphoria (Borras, Huguelet, & Eytan, 2007; De Cuypere, 1993). If this treatment is effective, the gender dysphoria will disappear (is the expectation) or remit [see the review of Marks, Green, and Mataix-Cole (2000); compare Marks and Mataix-Cole (1997)]. When the psychiatric disorder is more a consequence than a cause of the gender dysphoria (e.g., anorexia nervosa), it is sometimes effective to start with hormonal treatment anyway. By treating the gender dysphoria, the comorbidity may resolve or become less severe.

When gender dysphoria is a psychotic symptom or occurs in a psychotic episode, there is a worldwide consensus that sex reassignment therapy is contraindicated (e.g., WPATH, 2011). Also, in these cases, an effort must be made to improve the psychotic conditions first (e.g., with psychotropic medications). When, in a reevaluation of the patient's mental health status, the psychosis is deemed under control, but the gender dysphoria remains, a low-dose hormonal therapy (or antiandrogens) can be started. Risk factors and benefits will always be evaluated from a damage control perspective. Even if there is a close relation between another psychiatric disorder and gender dysphoria, it still may be indicated to start a sex reassignment treatment, if this intervention will lead to less gender dysphoria and as a consequence to more psychological stability of the person (e.g., Gijs & Brewaeys, 2007). Only when the psychosis is chronic and can't be kept under control, sex reassignment therapy will remain a contraindication. Mutatis mutandis, the same line of reasoning is followed for other severe psychiatric disorders as, for example, dissociative identity disorders (see vignette) or autism.

Unfortunately, until now, there is very little literature debating and arguing how to make decisions about therapy in these difficult cases (but see, e.g., De Cuypere, 1993; Mizock & Fleming, 2011).

13.4.2 Therapeutic Implications

Besides the diagnostic implications of comorbidity, there are also implications for the therapeutic relationship between the person with gender dysphoria and the psychological and/or medical professionals. In general, professionals have no gender dysphoria themselves and are not able to feel what gender dysphoria really means for a person. In that sense, it is not always easy for the therapist to empathize with the person with gender dysphoria. The occurrence of comorbidity may make this an even more challenging task for a clinician. How do therapists handle this task? We assume that most therapists are trying to be empathic toward their gender dysphoric patients but at the same time try to keep enough distance not to become gender confused themselves. We also assume that therapists who are counseling persons during gender reassignment are (mostly) not treating psychiatric comorbidity themselves, but are referring gender dysphoric patients to other specialized therapists to treat the psychiatric comorbidity. However, in our view, this approach runs the risk of splitting and iatrogenic pathology; splitting in the sense that the patient and therapist have different views on what is going on and what should be done and are struggling with each other to define what will happen. Iatrogenic pathology is an underestimated risk, which deserves much more attention [see also Mizock and Fleming (2011)]. Therapists working from a so-called dual or separate approach to each disorder, without taking their interrelations and the ways in which different therapeutic strategies are integrated into account, take the risk that they are creating more pathology instead of less. Sometimes gender dysphoric persons are told that their gender problems are not gender problems, but, for example, symptoms of borderline personality disorder (and vice versa).

13.4.3 Implications for Care After Sex Reassignment

To date, debates and discussions on the role of comorbidity in the diagnosis and treatment of gender dysphoria have mainly concerned the diagnostic phase and treatment until genital surgery. This approach might result from the viewpoint that a sex reassignment treatment will diminish or solve gender dysphoria [see also Levine and Solomon (2010)] as well as the co-occurring psychiatric disorder. And indeed, Murad and Colleagues (2010) found in their review of 28 follow-up studies that sex reassignment not only reduced gender dysphoria strongly but also improved psychological functioning significantly. However, some recent research shows that the prevalence of comorbidity after gender reassignment surgery is higher than expected from the perspective that hormonal and gender reassignment would lead to the disappearance of psychiatric comorbidity. Dhejne et al. (2011), for example, found, in a recent Scandinavian long-term study with a mean duration of approximately 10 years, that in transpeople, psychiatric comorbidity remained much higher than in the general population. However, this study, as most studies in this field (e.g., Gijs & Brewaeys, 2007), had several methodological limitations; they inferred an unjustified linear relationship between gender reassignment therapy and later quality of life, without taking into account the contributions of discrimination, stigma, oppression, and violence, and they neglected studies that did find positive outcomes. Also, this study provides no information with regard to the outcome if surgery was unavailable. However, we agree that care after sex reassignment should get a greater priority than it had until now, and we agree that clinicians should stay mindful of comorbidity after sex reassignment surgery [see also Levine and Solomon (2010)]. But we do not agree with their conclusions that sex reassignment is not an effective method for treating gender dysphoria. Most people who have undergone sex reassignment experience a drastic reduction of gender dysphoria (e.g., Gijs & Brewaeys, 2007; Lawrence, 2007; Lawrence & Zucker, 2012; Murad et al., 2010; Selvaggi & Bellringer, 2011). This is a result that no other treatment can claim until now. Furthermore, one should take into account that a hostile environment toward transgender people contributes to a higher prevalence of psychiatric disorders [and a lower quality of life; see also Kuhn et al. (2009)].

13.5 A Clinical Vignette

Jana, referred by her psychiatrist for a second opinion, was a 30-year-old person with a male body when she consulted a gender reassignment clinic for sex reassignment surgery. In a typical diagnostic procedure (regular monthly talks, writing a life story, completing a psychological test battery, and a heteroanamnesis), she told her clinician that she has felt gender deviant since she was 7 years of age. Now, after many years of struggling, she has found the courage and self-knowledge to go to a gender identity clinic. Her life has not been easy. She was sexually abused by her father and an uncle. She married when she was 18 and divorced when she was 25. She has two children. She has nearly no contact with her children and the contact with her ex-wife is very sporadic and negative. Furthermore, she has no work and has a slight, but permanent, cognitive impairment due to a traffic accident when she was working as a truck driver. The clinician was reluctant to advise his gender team to start with androgen deprivation therapy and estrogens to treat the strong and persistent gender dysphoria, despite the fact that Jana was living as woman for 3 years and that her well-being had greatly improved since the social transition to living as a woman, because he was worried about Jana's comorbidity. She has been diagnosed by many therapists with the following: dissociative identity disorder not otherwise specified, personality disorder not otherwise specified, with narcissistic and psychopathic traits, and as a person with a borderline personality disorder. She has been treated with different therapies with the result that her symptoms have become less severe. Furthermore, she has had problems with anger management and aggression regulation.

After a long diagnostic period (of approximately 3 years), the clinician thought that it was too risky to start a hormonal therapy. This was not so much based on the fear that the patient was psychologically insufficiently stable to undergo sex reassignment therapy, but because the therapist couldn't answer the question if the gender dysphoria was a symptom of the dissociative disorder (as was thought by her psychiatrist, in which the clinician has a lot of confidence). After consultation with a psychiatrist within the gender team who had the same doubts about the psychological stability of the patient, the team decided that there was too much uncertainty to start a hormonal treatment. An external specialist in dissociative disorders was asked for an independent diagnosis, in particular to answer the following question: Is the gender dysphoria a symptom of the dissociative disorder?

The answer of this specialist was very clear: The gender dysphoria is a symptom of another psychiatric disorder, however not so much of the dissociative disorder, but much more of the borderline personality organization, which has led to a very weak and very unstable identity. As a consequence, the advice was to treat the borderline personality disorder and not to start gender reassignment therapy. After consultation with her external psychiatrist, the gender team decided that it would not be wise to start a gender treatment. The communication of this message to the person led to a crisis in the therapeutic contact: The person could understand the carefulness and worries of the team but also felt deserted by the team. Nevertheless, Jana continued her contact with her psychiatrist and underwent an intensive treatment for her dissociative identity disorder and borderline personality disorder (with the expectation that her gender dysphoria would remit or at least would become much less intense). However, after 2 years, Jana was referred back to our team by her psychiatrist, who told us that Jana had been very compliant with therapy and had made good progress, but that her gender dysphoria had not disappeared. On the contrary, her female gender identity and gender dysphoria had grown stronger during therapy. Maybe, after all, a sex reassignment therapy was indicated. This time, the diagnostic procedure was much shorter. Although Jana still had psychiatric symptomatology, after a short period (approximately 4 talks during 4 months), the team reached a consensus that hormonal treatment was now indicated for Jana. She had always had a small social network, but has had a female partner for a few years, who is supporting her strongly.

After a successful real-life experience (of one year), the team agreed to gender reassignment surgery, very much to the delight of Jana. Nearly 10 years after her application/admission, she underwent gender reassignment surgery to create a neovagina, for which she longed for many years.

At this point, Jana is happy. She acknowledges that she still has psychiatric problems, but is very happy as a female (with breasts and a vagina).

13.6 Discussion and Conclusion

Conceptualizations of the “nature” of gender dysphoria have changed drastically during the last 50 years [see also Meyerowitz (2002)]. Three changes are paramount: (1) Gender dysphoria is no longer considered a symptom of another psychiatric disorder, (2) (hormonal or surgical) interventions to treat gender dysphoria are the most effective interventions today, and (3) people have a humanistic right to choose another gender or sex (Slatman & Widdershoven, 2009). Accordingly, clinical practice has also changed significantly. The crucial clinical questions no longer include the following: Of which psychiatric disorder is gender dysphoria a symptom, and which therapeutic intervention is necessary to restore normality or health? Health is no longer defined as accepting the sex of birth as normative for the gender identity (without gender dysphoria). Instead, the crucial questions have become the following: While people have a right to hormonal and/or surgical treatments for gender dysphoria, are there reasons to exclude an adult from a sex reassignment therapy (be it hormonal or/and surgical)?

Comorbidity is an important factor to consider in decisions of eligibility for sex reassignment treatment but even more in the counseling and treatment of gender dysphoric persons. In general, there is one reason with regard to comorbidity to exclude an adult from sex reassignment surgery: if gender dysphoria is solely/

mainly a symptom of another severe psychiatric disorder. In that case, the comorbid disorder will be treated first (or at least should be stabilized and controlled enough) with the expectation that gender dysphoria will disappear. If the gender problem is not a symptom of another psychiatric disorder per se, but the comorbidity is threatening the psychological stability and well-being of the person too much, one can start with hormonal therapy to see if the psychiatric comorbidity improves. Of course, this does not exclude psychotherapy or concurrent psycho-pharmacotherapy. Some clinicians, however, will prefer to require a certain level of psychological stability before starting with sex reassignment treatment.

Where do we go from here? Based on our view that people have an ethical right to be treated with hormonal and surgical interventions to diminish their suffering of gender dysphoria, and that sex reassignment treatments are the most effective treatments at the moment, we argue that it is necessary to improve our understanding of comorbidity and to give more effective care to people with gender dysphoria.

Some persons with gender dysphoria have psychiatric comorbidity before, as well as after, sex reassignment surgery. This comorbidity varies greatly, although the reasons for the variability are not well understood. We plead for future longitudinal research to understand the (determinants of the) interrelations between gender dysphoria and psychiatric comorbidity. From a developmental perspective, it seems especially imperative to study comorbidity before and after treatment for gender dysphoria, from adolescence through adulthood. From a sexological point of view, we know almost nothing about the sexual problems transgender people encounter pre- and post-sex reassignment surgery and how these problems are related to psychiatric comorbidity.

Therapeutically, studies about how to manage comorbidity to improve the effectiveness of sex reassignment surgery and the therapeutic relationship are urgently needed. So, our view on comorbidity can be summarized as follows: Let's be pragmatic, but also take comorbidity seriously. In doing so, we contribute to the well-being of our patients with GID.

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Chapter 14
Sex Reassignment: Endocrinological Interventions in Adults with Gender Dysphoria

Louis Gooren and Henk Asscheman

Abstract Transgender people may wish to transition to the other sex, usually to the fullest extent possible. Part of that transition is enabled by the administration of cross-sex hormones and part by surgical adaptation. The treatment of male-to-female transgender people consists of blocking androgen action and allowing estrogens to feminize the body. For virilization of female-to-male transgender people, androgens usually suffice. In adulthood, certain features of the sex hormone-induced body shape cannot be undone (such as the larger size of bones in males, the hip configuration in females). After about 2–3 years, the maximally attainable effects of cross-sex hormones have been reached. With competent endocrinological advice, cross-sex hormone treatment is usually uneventful. The estrogen ethinyl estradiol is to be avoided in view of the risks of venous thrombosis and cardiovascular disease. Androgen administration does not lead to an increase in cardiovascular disease. Hormone-dependent cancers have been observed in transgender people but not to an alarming degree. The relative rarity of transsexualism and the scattering of endocrine treatment over many centers is an impediment to build a solid body of knowledge with regard to efficacy and safety of cross-sex hormone treatment.

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14.1 Introduction

As elsewhere elaborately described in this Festschrift, transsexualism is the condition in which a person with apparently normal somatic sexual differentiation is convinced that he or she is actually a member of the other sex and believes she/he is trapped in the wrong body. This conviction is accompanied by the irresistible urge to live in that self-experienced gender, with a body that is not only anatomically as close as possible to that of the other gender but also psychologically, socially, and legally. According to current scientific evidence, transsexualism is an unalterable condition. For the affected individual, it represents a source of chronic suffering and disability. In this contribution, the principles of hormonal treatment of transsexual people will be discussed.

The indication for cross-sex hormone treatment is the result of psychological assessment that concludes that sex reassignment will bring relief to an individual suffering from gender dysphoria, the extreme feeling often described as being "trapped in the wrong body." Although endocrine treatment is recommended by a mental health professional, it is the prescribing physician who retains responsibility for the intervention and the quality of care. It is of utmost importance, then, that there is a close collaboration between the physician and the mental health professional. Sex reassignment (social, hormonal, surgical, and legal) is an ameliorative and rehabilitative treatment (Money, 1971). It is not a complete makeover of one's life. The only benefit sex reassignment can confer is relief of gender dysphoria; all human problems outside the area of gender dysphoria will remain, though overall well-being usually improves. Persons may harbor unrealistic expectations of hormonal and surgical treatment for transitioning to the other gender that must be addressed. Also, the limitations of cross-sex hormone administration on sex-typical body features in adult, and certainly elderly transsexuals, should be frankly discussed. After years of silent suffering and loneliness, fantasy often supersedes reality. Contact with others who are already in the process of transition, or who have completed this process, can be quite helpful in shaping a person's expectations of what can be reasonably achieved with hormonal and surgical treatment. Likewise, it will help the individual cope with the problems of transitioning (personal, professional, and social) that may arise, both initially and long term.

14.1.1 Cross-Sex Hormone Treatment

The administration of cross-sex hormones to transsexuals is, from the viewpoint of endocrinology, unorthodox. Therefore, cross-sex hormone treatment has for a long time met with reservation in professional medical circles, though acceptance is growing rapidly. Major textbooks such as Endocrinology (editors De Groot & Jameson, 2010), The Oxford Textbook of Endocrinology and Diabetes, and

Andrology for the Clinician (editors Wass & Shalet, 2011) now each have a chapter dealing with the issue of transsexual medicine.

The indication for hormone use is not based on standard technical endocrine grounds familiar to the endocrinologist, such as a deficiency or excess of hormone action. The endocrinological treatment was and is not standardized, and each attending endocrinologist has devised her/his own treatment schemes, usually based on principles of treating subjects with sex hormone deficiencies but now applied to the other sex. Both males and females have measurable levels of androgens and estrogens. In females, administration of testosterone is usually sufficient to induce virilization. In males, the high levels of testosterone block the biological actions of circulating estrogens, and in order to arrive at efficacious estrogen treatment, blood testosterone levels have to be suppressed or blocked in their biological action to almost nil.

The first reports detailing cross-sex hormone treatment of transsexuals appeared 40–50 years ago (Benjamin, 1966; Hamburger, 1969; Migeon, Rivarola, & Forest, 1968). In 1981, Meyer et al., (1981) published a survey of transsexual hormonal treatment in 20 gender-treatment centers and concluded:

> "*No systematic study has been published of the effects of hormonal therapy in the transsexual; specifically, its effect on physical changes, its suppression of endogenous hormones, or its side effects. With the growing number of transsexual treatment centers, it seemed timely to survey these programs and attempt to determine if a standard hormonal treatment exists. Twenty centers for transsexual treatment responded to a survey concerning their current hormonal treatment plan before and after removal of the gonads as sources of sex hormones. At least nine different male-to-female transsexual therapy programs and 11 different female-to-male transsexual testosterone therapy programs were reported. The typical program utilized, for male-to-female transsexuals, 2.5–5.0 mg/day of conjugated estrogen and, for female-to-male transsexuals, 200–400 mg of intramuscular long-acting conjugates of testosterone once a month. However, less than half of the centers are in agreement and the great diversity of therapies highlights the need for systematic studies of the effects of hormonal therapy to determine the optimal program for transsexuals.*"

In 2009, a task force of The Endocrine Society formulated guidelines for the endocrine treatment of transsexual people (Hembree et al., 2009), which is a major step forward. The guidelines specified dosage schemes of hormones, contraindications, recommendations for clinical follow-up, and warnings for short- and long-term side effects. The presently available knowledge about cross-sex hormone treatment did not allow evidence-based recommendations. The guidelines are based on clinical experience and general expertise in the area of sex hormone treatment (Wierckx, Mueller, et al., 2012; Wierckx, Stuyver, et al., 2012; Wierckx, Van Caenegem, et al., 2012).

14.1.2 General Aspects of Cross-Sex Hormone Treatment

Hormonal reassignment of adult persons has two aims: (1) to eliminate to the best degree possible the hormonally induced secondary sex characteristics of the natal sex and (2) to induce those of the new sex to the fullest extent possible. Secondary sex characteristics are contingent upon sex steroids. There is no known fundamental difference in sensitivity to the biological action of sex steroids on the basis of genetic configurations or gonadal status. Adult transsexuals undergoing sex reassignment have the disadvantage that, at that advanced age, a normal average degree of hormonal somatic masculinization or feminization has already irreversibly taken place. Unfortunately, the elimination of the hormonally induced sex characteristics of the natal sex is, therefore, rarely complete. In male-to-female transsexuals, the previous effects of androgens on the skeleton (the average greater height than women; the size and shape of the hand, feet, jaws, and male-type pelvis) cannot be reversed. Conversely, the relatively lower height of female-to-male transsexuals compared to men and the broader hip configuration will not change under androgen treatment. These features show a degree of overlap between the sexes, so, in some transsexuals, characteristics of the natal sex will be more visible than in others. Also, race is a significant determinant of sex differences in body configuration in adulthood, and, generally speaking, Asians transition physically more smoothly to the other sex than Caucasians, since Asians do have less pronounced secondary sex characteristics than Caucasians.

14.1.3 Male-to-Female Transsexual Subjects

For male-to-female transsexuals, elimination of sexual hair growth and induction of breast formation are essential. To attain both, an almost complete reduction of the effects of androgens is required. Administration of estrogens alone will suppress gonadotropin output and, consequently, androgen production, but dual therapy with one compound suppressing androgen action and another introducing estrogen is probably more effective. Several agents are available to inhibit androgen action. In Europe, the most widely used drug is cyproterone acetate (50–100 mg/day), a progestational compound with antiandrogenic properties. If not available, medroxyprogesterone acetate (5–10 mg/day), probably somewhat less effective, is an alternative. Nonsteroidal antiandrogens, such as flutamide (50–75 mg/day) and nilutamide (150 mg/day), are also used, but they increase gonadotropin output with a rise of testosterone and estradiol; the rise of estradiol is a desirable effect in this context. Spironolactone, a diuretic with antiandrogenic properties, widely used in the USA, has androgen receptor-blocking properties and also decreases testosterone production. Also luteinizing hormone-releasing hormone (LHRH) agonists, blocking LHRH receptors on the pituitary and decreasing LH production and therewith testosterone production, can be used as monthly injections. Finasteride 1 mg, which inhibits the conversion of testosterone to the much more biopotent 5α-dihydrotestosterone, now marketed for alopecia androgenetica (male-type hair loss), might also be considered.

There are a wide range of estrogens to choose from. Oral ethinyl estradiol (50–100 μg/day), the estrogen used in oral contraceptives, is a potent and cheap estrogen. It may increase the risk of venous thrombosis, particularly in subjects over 40 years (Toorians et al., 2003), and is associated with a threefold increase in cardiovascular mortality (Asscheman et al., 2011) and should therefore be avoided. Transdermal estrogens (100 μg 17β-estradiol/day) as a patch twice a week or oral estradiol esters (2–4 mg/day) are preferred. They are, however, less potent than ethinyl estradiol. Many transsexuals favor injectable estrogens; however, they generate high levels of circulating estrogens, with possible disadvantages, and they carry a higher risk of overdosing, which some transsexuals do.

As to the effects of this dual regimen of antiandrogens and estrogens, adult male beard growth is very resilient to the described hormonal intervention, and in Caucasian subjects additional measures (electrolysis, photothermolysis, laser light treatment) to eliminate facial hair are almost always necessary. Postpubertal sexual hair growth on other parts of the body responds more favorably, usually only waxing is required. Removal of sexual hair growth on the male genital structures, serving as tissue for the construction of female genitalia (vaginoplasty) by plastic surgery, may require additional measures, such as laser treatment. Breast formation starts almost immediately after initiation of cross-sex hormone administration and goes through periods of growth and standstill. Clinical experience shows that after 2 years of hormone administration, no further development can be expected. It is quantitatively satisfactory in 40–50 % of the subjects; the remaining 50–60 % judge their breast formation as insufficient. The attained size, only in 35 % cup B, is often disproportional to the existing male dimensions of the chest and height, and surgical breast augmentation may be desired. In the remaining 65 %, breast development is lower. Higher age may also impede full breast formation, though data are not very solid. Androgen deprivation leads to decreased activity of the sebaceous glands which may result in dry skin or brittle nails. There is an increase in subcutaneous fat deposits, and, following androgen deprivation, there is a loss of approximately 4 kg of lean body mass, but most of the time body weight increases. Testes, lacking gonadotropic stimulation, will become atrophic and may enter the inguinal canal which may cause discomfort.

After reassignment surgery, including orchiectomy, hormone therapy must be continued. Some subjects still experience an increased growth of male type of sexual hair, and antiandrogens appear to be effective, though their dose may be reduced compared to presurgery. Continuous estrogen therapy is required to avoid symptoms of hormone deprivation, most importantly, to prevent osteoporosis.

14.1.4 Female-to-Male Transsexuals

Androgen administration may decrease glandular activity of the breasts, but it usually does not reduce their size. The objectives of androgen administration are to stop menstrual activities, experienced as improper, and to induce a male pattern of sexual hair and male physical contours. Usually, this can be attained with administration of injections of testosterone enanthate or cypionate at a dose of

200–250 mg per 2 weeks or of late testosterone undecanoate 1,000 mg per 12 weeks. Occasionally, menstrual bleeding does not cease upon this regimen, and addition of a progestational agent is necessary. If other types of androgens are used (oral or transdermal), addition of a progestational agent is nearly always needed. The development of sexual hair essentially follows the pattern observed in pubertal boys: first the upper lip, then chin, then cheeks, etc. The degree of hairiness can usually be predicted from the degree and pattern in male members of the same family. The same applies to the occurrence of male pattern baldness. Deepening of the voice already occurs after 8–10 weeks of androgen administration and is irreversible. Androgen administration leads to a reduction of subcutaneous fat but increases abdominal fat storage. The increase in lean body mass, as a result of the muscle-promoting effects of androgens, amounts to 4 kg, but the increase in body weight is usually greater. Side effects are minor. In approximately 40 %, acne is observed, predominantly on the back, as is also the case in hypogonadal men starting androgen treatment past the age of normal puberty. Clitoral enlargement occurs in all, but to a varying degree; in a small number of subjects, the size becomes sufficient for vaginal intercourse with a partner. Most subjects will note an increase in libido. The ovaries show changes which are indistinguishable from polycystic ovaries. After surgical sex reassignment, including ovariectomy, androgen therapy must be continued to prevent symptoms of hormone deprivation, such as osteoporosis.

14.2 Concerns of Cross-Sex Hormone Administration

14.2.1 Bone Health

The evidence that adequate serum levels of sex steroids are required for formation of adult bone mass in the pubertal years and maintenance of bone mineral density in adulthood is overwhelming. Postmenopausal women, subjects with sex steroid deficiencies like Turner syndrome in women, Klinefelter syndrome in men, and prostate cancer patients treated with androgen deprivation treatment testify to the above. Therefore, bone health in people undergoing sex reassignment deserves attention. Since loss of bone mass (osteopenia/osteoporosis) is often perceived as a disease of women, there was a concern that FtM subjects receiving testosterone treatment would be at risk of developing loss of bone mineral density and, as a result, bone fractures. However, studies have indicated that testosterone administered in adequate doses is capable of maintaining bone mass in FtM persons (Turner et al., 2004; van Kesteren et al., 1996; van Kesteren, Lips, Gooren, Asscheman, & Megens, 1998). The protective effect of testosterone is likely, at least in part, mediated by peripheral conversion to estradiol both systemically and locally in the bone. But testosterone itself also has anabolic effects on bone mineral density, as demonstrated by a recent study. This study found larger radial cortical bone size and lower cortical volumetric bone mineral density at the radius and tibia in FtM subjects on testosterone therapy, compared to women (Van Caenegem et al., 2012). With regard to MtF persons, the question was whether estrogens-only were capable of maintaining bone mineral density. It was reassuring that studies in natal males suggest that serum estradiol more positively correlates with bone mineral density than testosterone and is more important for peak bone mass (Khosla, 2010). Studies have shown that estrogen adequately preserves bone mineral density in MtF persons who continue on estrogen and antiandrogen therapies (Mueller et al., 2005; Ruetsche, Kneubuehl, Birkhaeuser, & Lippuner, 2005), but a later study expressed some concern (T'Sjoen et al., 2009).

A very significant finding was that the adequacy of dosing of cross-sex hormone treatment can be estimated from serum levels of luteinizing hormone. The latter hormone, of which the levels are suppressed by the amounts of circulating sex steroids, should be in the range of eugonadal subjects (Turner et al., 2004; van Kesteren et al., 1998). Transsexual persons who discontinue cross-sex hormones are at risk of developing osteoporosis (van Kesteren et al., 1996). Transsexual subjects with risk factors for osteoporosis should be more intensively followed up. In the absence of specific recommendations for transsexual people, the guidelines for the general population may be used (Ballantyne, Kayser, & Grootegoed, 2011; Watts et al., 2012).

14.2.2 Venous Thromboembolic Disease

A major side effect of cross-sex hormone treatment in MtF subjects is the increased risk of venous thromboembolism (VTE). Thrombotic events in MtF subjects on estrogen therapy such as pulmonary embolism and cerebral thrombosis have been reported from early on. In 1989, the VU university gender identity clinic reported a 45-fold increase in the incidence of VTE among 303 MtF subjects treated with oral ethinyl estradiol 0.1 mg/day + cyproterone acetate 100 mg/day compared to nonusers (Asscheman, Gooren, & Eklund, 1989). In the subjects of this study, no other known risk factors, such as surgery or immobilization, were found in 13 out of the 19 cases of VTE. The risk appeared clearly associated with age (2.1 % <40 years and 12 % >40 years of age). In a second study with a larger number of MtF subjects ($n = 816$) and longer follow-up (mean 9.5 years), drawing lessons from the earlier study, incidence of VTE had become lower after the introduction of transdermal estrogen as standard therapy in all MtF subjects >40 years of age, but the VTE incidence was still 20-fold increased ($n = 45$), and 36 VTE events (35 on ethinyl estradiol, 1 on transdermal estradiol) occurred in the absence of other known risk factors (van Kesteren, Asscheman, Megens, & Gooren, 1997). Remarkably, in both studies, the majority of VTE cases were diagnosed in the first year of estrogen treatment. Postoperative VTE prevalence was 1.7 % in the 1989 study (Asscheman et al., 1989) and <1.0 % in the 1997 study (van Kesteren et al., 1997), probably due to the introduction of postoperative thrombosis prevention with low molecular weight heparin for all surgery in the 1980s. In a third study of the VU university gender identity clinic, it could be demonstrated that oral ethinyl estradiol 0.1 mg/day combined with cyproterone acetate 100 mg/day caused a large increase in activated protein C (APC) resistance (nAPCsr increased from 1.2 ± 0.8 to 4.1 ± 1.1), thus increasing the risk of thrombosis, but transdermal estradiol 100 μg patch 2×/week + cyproterone acetate 100 mg/day or cyproterone acetate alone had only a small effect on APC resistance (1.3 ± 0.6 to 2.0 ± 2.0 and 1.4 ± 0.6 to 1.8 ± 0.9, respectively). Moreover, ethinyl estradiol + cyproterone acetate also decreased protein S levels, an inhibitor of coagulation. In a group of 20 subjects on oral estradiol-17β 4 mg/day + cyproterone acetate 100 mg/day, APC resistance was not different from the values on oral cyproterone acetate, with or without transdermal estradiol. It was concluded that the prothrombotic effect of ethinyl estradiol is due to its molecular structure rather than to the first-pass liver effect which ethinyl estradiol shares with all oral estrogens (Toorians et al., 2003).

A recent literature search in PubMed resulted in nine papers that mentioned VTE as a complication of cross-sex hormone treatment mainly with estrogen-only treatment and reported on numbers and period of follow-up in estrogen-treated MtF subjects. We found only two studies with a relatively large number of user-years, the one from Amsterdam 1997 (van Kesteren et al., 1997) [which is an extension of the 1989 study (Asscheman et al., 1989) as described above and a study from Vienna (Ott, Kaufmann, Bentz, Huber, & Tempfer, 2010)]. All other studies had small numbers of user-years and few thromboembolic events resulting in very wide confidence intervals, precluding firm conclusions about the VTE risk in these populations.

In 2010, we sent questionnaires to nine European Gender Centers that treat large numbers of MtF people. These questionnaires enquired about the number of confirmed cases of VTE in MtF subjects treated with cross-sex hormone treatment and about the type of cross-sex hormone treatment. Cases of VTE had been diagnosed in all centers. Prevalence rates of any VTE during the whole follow-up period varied from 0.3 to 3.5 % of MtF subjects treated with cross-sex hormone therapy per center. Incidence rates of VTE varied from 4.8 to 35.7 per 10,000 user-years. The summary statistics with the random effects model yielded a weighted mean incidence rate of 13 per 10,000 user-years (95 %CI, 4–22), much higher than among users of oral contraceptives.

Remarkably, at least four VTE events out of 21 occurred in MtF subjects on oral contraceptives containing ethinyl estradiol + cyproterone acetate (19 %), three on transdermal estradiol with cyproterone acetate, four on oral estradiol (one on 2 mg/day, one on 4 mg/day after immobilization, and two on the high dose of 6 mg/day), and one on conjugated estrogens 0.625 mg/day (rarely used in Europe). In six cases, the type of hormone treatment at the time of the thrombotic event could not be assessed, but use of oral contraceptives was probable in four. Presuming the last four did use oral contraceptives, this would imply that ethinyl estradiol was the main culprit in eight (38 %) of the 21 confirmed events of VTE, but, of course, the latter presumption cannot be confirmed.

Postoperative VTE was rarely reported in our questionnaire, but many clinics had data on less than 100 cases of sex reassignment surgery (SRS) and all used low molecular weight heparin thrombosis prophylaxis during about 30 days postoperatively.

It was concluded that prevalence and incidence rates of VTE in estrogen-treated MtF persons have decreased considerably but are still elevated compared to the general population and also compared to women using oral contraceptives and estrogen replacement treatment (6–8/10,000 user-years). The data allowed some recommendations to be made: The use of ethinyl estradiol (and ethinyl estradiol containing oral contraceptives) is to be avoided. Use of transdermal patches or gel (the latter carries some risk of overdosing) or low to intermediate doses of oral estradiol (2–4 mg/day) or conjugated equine estrogens (up to 2.5 mg/day) is recommended. Cross-sex hormones should probably be discontinued before elective surgery for at least 2 weeks and resumed after 3 weeks and full mobilization.

14.2.3 Metabolic Aspects of Cross-Sex Hormone Administration and Cardiovascular Health

Cardiovascular disease is more common in males and the risk in women increases only after menopause with its cessation of estrogen production. The skewed sex ratio in cardiovascular disease has been interpreted to indicate that estrogens are cardioprotective and that androgens might increase cardiovascular disease. However, the large randomized trials (Heart and Estrogen/Progestin Replacement Study (HERS) and the Women's Health Initiative) have refuted the protective effect of exogenous estrogens in women (Grady & Barrett-Connor, 2007). Cross-sex hormone administration in both MtF and FtM persons both improves and impairs profiles of cardiovascular risk factors. It remains difficult to determine how much weight should be attributed to these alterations in risk factors and whether these changes are of clinical significance. With these reservations in mind, the overall impression is that inducing androgen deprivation and an estrogen milieu in MtF subjects has a larger deleterious effect on risk factors than inducing an androgenic milieu in FtM subjects (Gooren & Giltay, 2008; Gooren, Giltay, & Bunck, 2008).

Data on clinical endpoints from the morbidity and mortality study in 1997 (van Kesteren et al., 1997) showed no elevated (cardiovascular) morbidity and/or mortality in the cohort of transsexuals treated at the Amsterdam clinic. More recently, two cohort studies on mortality in hormone-treated MtF persons with much longer follow-up reported an increased cardiovascular mortality. In the Amsterdam cohort, standardized mortality from ischemic heart disease was clearly increased (SMR 1.64) and associated with ethinyl estradiol use, more smoking, and hyperlipemia (Asscheman et al., 2011). In androgen-treated FtM subjects, no increased cardiovascular mortality was observed. In a Swedish cohort, the hazard ratio of cardiovascular death was 2.5 (Dhejne et al., 2011).

To reduce the risk of cardiovascular death, use of ethinyl estradiol should be avoided, and, for all transsexual persons' lifestyle behaviors, healthy diets, smoking cessation, and regular exercise are recommended.

14.2.4 Partial Sex Reassignment

The World Professional Association for Transgender Health (WPATH) has updated the Standards of Care (SOC) (7th edition, July 2012) (www.wpath.org/documents). The overall goal of the SOC is to provide clinical guidance for health professionals to assist transsexual, transgender, and gender nonconforming people with safe and effective pathways to achieving lasting personal comfort with their gendered selves, in order to maximize their overall health, psychological well-being, and self-fulfillment. The scope of SOC has widened to those subjects who need and wish only partial sex reassignment treatment, which may consist of blocking the action of sex hormones of their natal sex (with hormone-blocking agents or surgery) without using cross-sex hormones. Endocrinologically speaking, a functional status of hypogonadism is induced. Prominent symptoms to arise are loss of bone mass (osteopenia, osteoporosis), loss of muscle mass, obesity, and lipid disorders increasing cardiovascular risks. These interventions must not be undertaken without medical supervision to mitigate the consequences of the induced hypogonadism. In particular, the group seeking limited adaptation to the other sex may fall outside the established categories in gender identity clinics and may be inclined to self-medicate.

14.2.5 Illicit Use of Cross-Sex Hormones

It is not rare that transgender individuals face harassment, discrimination, and rejection, not only in society but also in the medical system. Lack of awareness, knowledge, and sensitivity in healthcare communities eventually leads to inadequate access to, underutilization of, and disparities within the healthcare system for this population. The Institute of Medicine has published a book detailing the health needs of, among others, transgender people (Institute of Medicine, 2011), highlighting the significance of minority stress on health. Transgendered individuals may be frustrated with the standards of care that most recognized gender identity clinics observe, and there may be long delays before cross-sex hormone treatment is actually initiated. There may be financial barriers to undergo treatment in these centers. It is, therefore, not rare that transsexuals self-medicate with cross-sex hormones. Cross-sex hormones are affordable and relatively easily obtainable from peers or from the Internet. Many individuals in these situations receive advice on the use of hormones from peer groups. There is little documentation of illicit use of cross-sex hormones. In one Spanish study, there were several medical side effects that needed medical interventions (Becerra Fernandez, De Luis Roman, & Piedrola Maroto, 1999). Another study from Thailand found that about 50 % of subjects use hormones in overdose (Gooren, Sungkaew, & Giltay, 2012).

14.2.6 Tumors in Transsexuals Receiving Cross-Sex Hormones

A large number of transsexuals receive cross-sex hormone treatment from a relatively young age, and over their lifetime, they are exposed to cross-sex hormones for several decades. The dose taken is most of the times higher than the standard sex hormone replacement treatment in hypogonadal people. There is no evidence that men and women differ in sensitivity to the hormone action of sex steroids. Relationships exist between exposure to sex hormones and tumors of the reproductive organs, but a number of other tumors of nonreproductive organs appear to be sensitive to the action of sex steroids also. These tumors and the organs from which they originate sometimes have receptors for sex steroids. Examples are tumors of the lung (adenocarcinoma, small cell carcinoma) (Dougherty et al., 2006), of the colon (Slattery et al., 2006), of the bladder (but the latter mainly in animal models), and of the brain, particularly meningiomas (Wigertz et al., 2006).

After a successful transition to the new sex, transsexuals may not always be forthright with physicians about their past sex change, and this can lead to delays in diagnosing cancers of organs specific to the former sex. Hormone-dependent tumors appear to be rare in transsexual persons, but there may be an increase in the future. Aging may be a factor in their development, and, also, the increasingly longer duration of sex hormone administration in people having undergone sex reassignment at a young age may lead to an increase of tumors in the near future. It is difficult to reliably assess the prevalence of tumors in transsexuals. As indicated above, these tumors are relatively rare, as is transsexualism. Establishing a (potentially causal) relationship would require case–control analyses in large population cohort studies. For a review on tumors in transsexual persons receiving cross-sex hormones, see Mueller & Gooren, 2008.

In most European countries, transsexual persons receive surgical sex reassignment usually 18–36 months after start of cross-sex hormone treatment, thanks to the fact that surgical sex reassignment is covered by their health insurance. But in other parts of the world, including the USA, this may not be the case. There is no documentation of complications arising from this situation, but on the basis of insights into the pathogenesis of certain malignancies, some concern seems to be justified.

14.2.6.1 Tumors in Male-to-Female Transsexual Subjects

- Lactotroph adenoma of the pituitary gland (prolactinoma)
  There are several reports on prolactinomas in transsexual people in the literature. Initially, the impression was given that they occurred following very high dosages of estrogens (Gooren, Assies, Asscheman, de Slegte, & van Kessel, 1988; Kovacs, Stefaneanu, Ezzat, & Smyth, 1994; Serri, Noiseux, Robert, & Hardy, 1996), but later reports document that this need not be the case (Garcia-Malpartida, Martin-Gorgojo, Rocha, Gomez-Balaguer, & Hernandez-Mijares,

2010). Prolactinomas may present themselves after long-term estrogen administration, stressing the importance of prolactin levels being checked over the long term, be it with low frequency (Bunck et al., 2009). Hearsay suggests that prolactinomas may be more prevalent than have been reported.

- Breast cancer
  Breast cancer has been reported in six cases (Ganly & Taylor, 1995; Pritchard, Pankowsky, Crowe, & Abdul-Karim, 1988; Symmers, 1968). It is remarkable that these cases occurred more than 15 years ago, but there are also more recent cases (Dhand & Dhaliwal, 2010; Grabellus et al., 2005). The number of transsexual people receiving cross-sex hormones has increased substantially; however, there remains a relative paucity of breast cancer in MtF subjects, which may have a parallel with sufferers of Turner's syndrome who are receiving estrogen treatment; the risk of breast cancer in these subjects is also very low (Schoemaker, Swerdlow, Higgins, Wright, & Jacobs, 2008).
- Prostate cancer
  Against expectations, prostate carcinoma was found in five cases of MtF subjects receiving estrogen treatment. In three cases, cross-sex hormone treatment only started after the age of 50 years, and the carcinoma may already have been present without generating clinical complaints (Dorff, Shazer, Nepomuceno, & Tucker, 2007; Thurston, 1994; van Haarst, Newling, Gooren, Asscheman, & Prenger, 1998). In two other subjects, this appeared not to be the case, however (Miksad et al., 2006; Molokwu, Appelbaum, & Miksad, 2008).
- Meningioma
  After the one case mentioned in the literature (Gazzeri, Galarza, & Gazzeri, 2007) occurring after 3 years of antiandrogen and estrogen treatment, two others have been reported. One in an MtF subject developed after initiation of hormone therapy (Deipolyi, Han, & Parsa, 2010), one that regressed after discontinuation of cyproterone acetate treatment (Cebula, Pham, Boyer, & Froelich, 2010).

14.2.6.2 Tumors in Female-to-Male Transsexual Subjects

- Vaginal carcinoma
  One case was reported 18 years after surgical sex reassignment treatment with partial removal of the vagina (Schenck et al., 2010).
- Ovarian cancer
  There have been three instances of this cancer (Dizon, Tejada-Berges, Koelliker, Steinhoff, & Granai, 2006; Hage, Dekker, Karim, Verheijen, & Bloemena, 2000). In testosterone-treated FtMs, the ovaries usually increase in volume and display characteristics of polycystic ovaries (Grynberg et al., 2010; Pache & Fauser, 1993). It is not certain whether these changes carry a higher risk for malignant development (Galazis, Olaleye, Haoula, Layfield, & Atiomo, 2012).
- Endometrial cancer
  Endometrial atrophy has been noted in 45 % of testosterone-treated FtMs (Grynberg et al., 2010). Although endometrial cancer has never been reported in FtMs, it could occur in those who have not undergone surgical sex reassignment, including

hysterectomy. Administered testosterone is partially aromatized to estrogens, and estrogen action on the endometrium unopposed by progesterone increases the risk of cancer development. Addition of a progestin may be useful, though that may increase the risk of breast cancer (Ito, 2007) if the breasts have not been removed. The role of testosterone in the pathogenesis of endometrial cancer is not clear (Mueller & Gooren, 2008). A case of a preinvasive cervical carcinoma after performed hysterectomy has been reported (Driak & Samudovsky, 2004).

- Breast carcinoma

  In testosterone-treated FtMs, there is usually a marked reduction of glandular tissue and an increase of fibrous connective tissue (Slagter, Gooren, Scorilas, Petraki, & Diamandis, 2006). However, as previously indicated, administered testosterone is partially aromatized to estradiol, and this can be a risk factor for FtMs who have not undergone mastectomy. Two cases of breast cancers have been diagnosed in FtM persons who have been treated with supraphysiological doses of testosterone, suggesting the possible role of testosterone in the development of breast cancer (Shao, Grossbard, & Klein, 2011).

  Even those who have undergone mastectomy may still retain some vulnerability, and one case of cancer has been reported in residual breast tissue 10 years after the breasts were removed (Burcombe, Makris, Pittam, & Finer, 2003). It appeared that there was a strong positive family history of breast cancer in this case. A recent study has also found an association between testosterone administration to FtMs and breast cancer-related gene expression signatures (Bentz et al., 2010). It is not yet clear what the role of testosterone is in the pathogenesis of breast cancer. It may certainly have a role, especially in postmenopausal women (Baglietto et al., 2010), though there is not yet general agreement on this (Dimitrakakis & Bondy, 2009).

14.3 Reproductive Health

When sex reassignment of transsexual people became a more accepted practice in medicine, it was almost axiomatic that, with the hormonal and surgical transition to the other sex, the procreative potential was irreversibly lost. This was "the price to pay" for becoming a member of the other sex (De Sutter, 2001).

Over the last two decades, there have been profound changes in the thinking about the ethics of reproduction, and it is now widely accepted that every person has the fundamental right to procreate. With regard to transsexual people, it has been argued that opting for the treatment they undergo, they forfeit the right to procreation. But the thinking about transsexualism has progressed, and it is now well understood that sex reassignment of transsexual people is not optional and is vital for their well-being. Presently, it is felt that transsexual individuals are in the same position as others whose procreative potential is jeopardized by their medical treatment, such as people with malignancies undergoing treatment with cytotoxic drugs or radiation. All these categories need to be counseled on the consequences of their medical interventions, and they must receive information on options to preserve their procreative potential, well before the interventions take place. For MtFs, this involves banking of spermatozoa and, for FtMs, the banking of oocytes, embryos, and ovarian tissue (Wierckx, Mueller, et al., 2012; Wierckx, Stuyver, et al., 2012; Wierckx, Van Caenegem, et al., 2012).

14.4 Transsexual People and Competitive Sports

After sex reassignment, transsexual people like to merge with the general population and lead the lives of ordinary men and women. Competition in sports may be part of that life. Sex segregation in competitive sports is regarded as fair. Boys and girls hardly differ before puberty in physique: Height, muscle, and bone mass are similar. In boys, exposure to testosterone during puberty produces an ultimate average greater height in men of 12–15 cm, larger bones, greater muscle mass, increased strength, and higher hemoglobin levels. Androgen ablation in postpubertal life reverses, at least in part, previous anabolic effects of testosterone on muscle (Mauras et al., 1998), bone mineral density, and hemoglobin, but the bones remain longer and have a wider diameter. It has been shown that treatment with testosterone produces a dose-dependent increase in muscle mass and maximal voluntary strength (Choong, Lakshman, & Bhasin, 2008; Storer et al., 2003), and therefore, sport organizations have banned androgens being performance-enhancing drugs (Handelsman & Heather, 2008). If men suffer from testosterone deficiency, testosterone replacements are permissible provided they do not raise blood testosterone levels above the normal male range (Gooren & Behre, 2008; Handelsman & Gooren, 2008).

Before the year 2000, genetic markers were used to determine sex for competition in sports. Chromosomal criteria of sex alone are not good indicators for differences in strength to ensure fair competition. In humans, there is no evidence that the pattern of sex chromosomes has a direct effect on muscle mass and strength. It is mainly testosterone that determines muscle mass and strength in a linear fashion. Therefore, in sports, exposure to androgens, previous and present, is a reasonable criterion for deducing unfair competition, not only between men and women but also between men.

Of late, sport organizations have addressed the issue of the participation in competitive sports of people with errors of sexual differentiation and particularly transsexual people who have been sex-reassigned. First of all, it is relevant, in view of the effects of testosterone, whether sex (re)assignment occurred before or after hormonal puberty. People who have had sex reassignment before puberty are still rare but their number will grow. Studies in the rat have shown that genetic configuration and gonadal status have no known significant effect on receptor-medicated actions of testosterone (Bentvelsen et al., 1995). During puberty, testosterone has a profound effect on bone and muscle mass and strength. Upon withdrawal of testosterone, the effects of testosterone are certainly in part reversible, but the precise extent is unknown (Gooren & Bunck, 2004). When muscle surface areas, measured by magnetic resonance imaging of male-to-female transsexuals and female-to-male transsexuals, were compared, there was a significant difference in the mean values, but there was also a considerable overlap between the two groups before any hormonal intervention had taken place. Androgen deprivation in MtF persons reduced muscle surface area, but still, after 1 year, the mean muscle surface area in male-to-female transsexuals remained significantly greater than in untreated female-to-male transsexuals; again, the two groups showed substantial overlap. As expected, testosterone administration to female-to-male transsexuals produced a significant increase in muscle surface areas. There was a large overlap with untreated male-to-female transsexuals, but the mean was significantly lower (Gooren & Bunck, 2004). Cross-sex hormones had effects on insulin-like growth factor and hemoglobin levels, both relevant for sports, in the same direction as the changes in muscle surface area.

It seems appropriate to place the effects of hormonal interventions in transsexuals in the perspective of naturally occurring differences in sporting capability between members of the same sex. While unfair competition should be prevented as much as possible, ultimately nature is unfair in her endowments of talents for all walks of life.

The International Olympic Committee (IOC) has drawn a necessarily arbitrary line which, based on present information, is reasonable with regard to participation of sex-reassigned transsexuals: Sex reassignment must have taken place at least 2 years earlier. In our aforementioned study, it could be shown that changes in muscle surface area were not greater after 3 years of cross-sex hormone administration than after 1 year (Gooren & Bunck, 2004). As is the case with hypogonadal men, doses of testosterone administered to female-to-male transsexuals must be in normal male range. Further, the reassigned sex must be legally recognized. The IOC policy is not binding for other sports organizations.

14.5 Thoughts About Past, Present, and Future of Cross-Sex Hormone Therapy

As indicated above, clinics offering cross-sex hormone treatment have largely developed their own treatment schedules, usually based on personal experience and personal insights into the workings of cross-sex hormones on persons of one sex wishing to transition to the other sex. It is not realistic to believe that the situation has greatly improved in 2012, although the guidelines of The Endocrine Society formulated by a panel of experts signify a step forward (Hembree et al., 2009). It is unrealistic to believe that studies with a rigorous design that can arrive at evidence-based guidelines can be performed. Second best are large cohort studies of hormone-treated transsexual people. Prospective studies with hormonal interventions based on treatment protocols and safety measurements would be desirable but are still in an early phase of development, and results are not expected for many years. Moreover, specific knowledge about effects of treatment in older subjects (>50 years of age) and long-term effects (>15 years of hormone use) or the risk of different hormone regimens will not be available in the near future. Retrospective cohort studies could bridge this gap: Transgender persons have been treated and followed up in multidisciplinary gender teams which have come into existence over the last 20 years.

A number of them have published some of their results, but the comparatively low numbers of subjects relative to other conditions (with rough estimates of prevalence around 1:10,000 MtF persons and 1:25,000 FtM persons), different (hormonal) treatment protocols, and low number of exposure-years preclude firm conclusions. A strategy dubbed as “incremental validity” may be that of combining the existing data of those gender teams, a dataset with sufficient numbers of hormone-treated subjects with different hormonal regimens and longer follow-up time, resulting in a large number of treatment-years. Analysis of this dataset can ascertain the incidence of side effects and comorbidity by type of hormone therapy, period of follow-up (especially after more than 15 years of hormone use), age groups (in particular those over 50 years of age), and the relation with (cardiovascular) risk factors. The authors are involved in a study aiming to fill the gaps in knowledge about side effects, bone health, and cardiovascular risk factors which could be extended to other domains of health of people receiving cross-sex hormones.

Side effects in the short and medium term have been charted, and cross-sex hormone treatment seems acceptably safe (Asscheman et al., 2011; Gooren, 2011; Gooren et al., 2008; Gooren & Giltay, 2008; Hembree et al., 2009). There is no substantial information of long-term use of cross-sex hormones. The question is whether findings in natal men and women can reliably be extrapolated to the transsexual population. Elderly men with testosterone deficiency have a high risk of mortality due to, for instance, metabolic syndrome (Haring et al., 2009; Yeap, 2009; Yeap et al., 2009). Is the lesson that FtMs should continue testosterone until a very advanced age? Conversely, what should be the recommendation for aging MtF persons? The sudden decision by the National Heart, Lung, and Blood Institute of the National Institutes of Health to terminate the estrogen-progesterone therapy arm of the Women’s Health Initiative (WHI) study a decade ago gave rise to major concerns about safety (Grady & Barrett-Connor, 2007). They are, however, now pleased to reconsider this abrupt decision (Utian, 2012). A recent Cochrane review concluded that hormone therapy is not indicated for primary or secondary prevention of cardiovascular disease or dementia nor for preventing deterioration of cognitive function in postmenopausal women. Although hormone therapy is considered effective for the prevention of postmenopausal osteoporosis, it is generally recommended as an option only for women at significant risk, for whom non-estrogen therapies are unsuitable (Marjoribanks, Farquhar, Roberts, & Lethaby, 2012). With regard to MtF persons, careful follow-up should guide hormone treatment of aging MtF persons.

Most providers of cross-sex hormone treatment will agree that a substantial part of the transsexual population will act as shareholders with an activist attitude with regard to their treatment. It is probably an expression of the deep suffering these people have gone through and the big stakes they have in a better future life in the new sex. Naturally, this cannot be divorced from the profound changes patient–doctor relationships have undergone in the past decade. Doctors are not infallible and there should be no problem in publicly acknowledging this. Patients have access to medical information available on the Internet and may attribute greater significance to this information than warranted. The information is as reliable as those who put the information on the Internet, some of whom have an activist attitude that privileges personal opinion over scientific facts. It is regrettable and detrimental when the patient–doctor relationship becomes adversarial. An example is the use of progesterone-like drugs in the treatment of MtF persons. While progesterone is an essential hormone for reproductive functioning of women (preparing the uterus for implantation of the fertilized egg and the breasts for lactation, therefore a "female" hormone), it has, on the basis of present knowledge, no meaning for the feminization of MtF persons and may have detrimental effects on general health (Zitzmann, Erren, Kamischke, Simoni, & Nieschlag, 2005). Yet, it is not rare that MtF persons insist on taking the second female hormone, progesterone, in addition to estrogens.

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Chapter 15
Surgical Interventions for Gender Dysphoria

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Abstract For individuals with pronounced gender dysphoria, surgery is the ultimate and the most radical step in the process of gender reassignment and follows a period of real-life experience and hormone treatment.

In this chapter, a complete overview is first provided of all surgical procedures, both in male-to-female and female-to-male transsexuals: These include aesthetic operations, breast surgery, and genital surgical interventions.

For the male-to-female individual, a more in-depth description is provided of facial feminizing surgery (FFS), of breast augmentation, as well as of the different techniques for vaginal reconstruction. Emphasis is placed on functional outcomes, on the reduction of complications, and on aesthetic improvements.

In the female-to-male transsexual, the subcutaneous mastectomy (SCM) or male chest contouring and the different surgical options for phalloplasty or penile reconstruction are described in more detail. The advantages and disadvantages of the different techniques are addressed.

It is concluded that in order to obtain optimal results in transgender surgery, a close cooperation between the different professionals involved is an absolute requirement.

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15.1 Introduction

Most professionals nowadays concur that gender reassignment, or “adjusting the body to the mind,” is the best way to assist severely gender dysphoric persons who desire this procedure (Cohen-Kettenis & Kuiper, 1984; Kuiper & Cohen-Kettenis, 1988). Surgery is the ultimate and the most radical step in the process of gender reassignment and follows a period of living in the desired gender role and hormone treatment.

While it might seem that gender reassignment surgery (GRS) would be the inevitable conclusion to gender reassignment, and sought in virtually every case, a significant number of persons who make gender transitions never undergo surgical reassignment. In some cases, this is by choice and, in other cases, by necessity. Still, for most transsexual persons, sex reassignment surgery remains the sine qua non of the reassignment experience since having congruent genitalia is considered essential for the transsexual individual to experience harmony between body and self-identity.

The Standards of Care (SOC) of the World Professional Association of Transgender Health (WPATH) are clinical guidelines intended to provide flexible direction for the treatment of persons with gender identity disorders. These standards are adopted worldwide by most professionals and clearly delineate the indications and the different options for sex reassignment surgery (Coleman et al., 2011). Of course, the availability of professional services, mental health as well as medical professionals, varies enormously per country or state.

The criteria for breast (top) surgery differ from those for genital (bottom) surgery since only one letter of recommendation is required for a breast augmentation or a subcutaneous mastectomy and two letters are required prior to genital surgery. By following this procedure, the mental health professional, the surgeon, and the patient share the responsibility for the decision to perform irrevocable surgery.

As to the requirements for the surgeon, the SOC of WPATH specify that the surgeon performing genital surgery should be a medical board-certified urologist, gynecologist, plastic surgeon, or general surgeon, with specialized competence in genital reconstructive techniques, as indicated by documented supervised training with a more experienced surgeon.

Long-term postoperative follow-up, one of the factors associated with good psychosocial outcome, is strongly encouraged. Such follow-up is important for the patient’s further health and provides the surgeon with continuous feedback regarding the benefits and limitations of surgery.

Finally, the need for collaborative care cannot be stressed enough. No single medical specialty can provide comprehensive care to the transsexual patient. Gender dysphoria is a multifaceted condition requiring a multidisciplinary approach. This is particularly true when surgical procedures require several specialists participating simultaneously in the operating suite.

15.2 Sex Reassignment Surgery in the Male-to-Female Transsexual

15.2.1 History of Gender Reassignment Surgery Among Male-to-Female (MtF) Transsexuals

Although Abraham (1931) was the first to describe an intentional sex change operation in a transsexual patient in 1931, this was certainly not the first use of surgery to relieve the agony of persons with irreversible gender dysphoria (Edgerton, 1984). People throughout the world have voluntarily undergone surgery, in the sense of "traumatic alterations," to modify their bodies in such a way as to "change their sex."

Accumulating knowledge of the effects of castration, as witnessed in animals, has been applied to help male-to-female (MtF) transsexuals. Eunuchs have existed since biblical times, and it is unknown to as what extent their castrations were voluntary. It is quite likely that hundreds or thousands of transsexuals have sought and undergone surgeries far riskier and more dramatic in effect than mere castration. In some such surgeries, transsexuals were completely emasculated by total removal of the testes, penis, and scrotum. It is unknown when such practices first occurred, but such surgeries were recorded in ancient Greece and particularly in Rome, known for being sexually permissive.

In personal diaries of the seventeenth century, two rather crude, self-inflicted operations were described as providing great and lasting subjective relief of gender dysphoria. These emasculating tactics were suppressed in the Christian world (with the exception of the castration of boys to maintain voice quality), but in Asia they have continued uninterrupted to the present, notably in South-East Asia, India (e.g., the Hijra), and surrounding countries (Monstrey, Selvaggi, & Ceulemans, 2007).

Prior to the second half of the twentieth century, there were legal restraints prohibiting the modification of gender by surgery. These restrictions loosened considerably in the latter half of that century only then resulting in the development of modern gender reassignment surgery. With rapid advances in the fields of endocrinology and plastic surgery following World War II, comprehensive medical and surgical treatments for transsexualism became available. Indeed, during the 1950s, transsexual women benefited enormously from newly available female sex hormones, which fostered breast development, softening of the skin, and, in time, female body contours.

The first vaginoplasty in a MtF transsexual was performed in Denmark in 1952 with a skin graft, but it was Dr. G. Burou (1973), a French gynecologist working in Casablanca, Morocco, who has been credited with the invention of the anteriorly pedicled penile skin flap inversion technique as the technique of choice (still nowadays) for vaginoplasty in MtF transsexuals. In this technique, the penile skin is kept attached at the pubic region and is invaginated into the newly created vaginal cavity. Except for Casablanca, access to this new, experimental surgery was very limited, and in the USA, despite the groundbreaking work of Harry Benjamin (1966), an endocrinologist with a specific interest in transsexualism, these surgeries were still virtually unknown in the mid- to late 1960s.

In 1966, surgeons at the Johns Hopkins Medical Centre began performing a limited number of MtF gender reassignment surgery (GRS) operations, and a couple of years later, they were followed by surgeons at Stanford University and in Trinidad, Colorado.

In Europe, beginning in the 1970s, the University Hospital of the Free University of Amsterdam (now called the VU University Medical Center) became the leading center in medical and surgical treatment of patients with severe gender dysphoria, under the leadership of Louis Gooren, endocrinologist, and F. Bouman, plastic surgeon. Their successors Peggy Cohen-Kettenis and Joris Hage further expanded the lead of Amsterdam in the treatment of transsexualism.

15.2.2 Overview

MtF gender reassignment surgery can be classified into three categories:

1. *Nongenital, non-breast* surgical interventions: Facial feminizing surgery, liposuction, lipofilling, gluteal implants, reduction of the Adam's apple, voice-raising surgery, hair reconstruction surgery, and various other cosmetic procedures
2. *Breast* (top) surgery: Augmentation mammoplasty
3. *Genital* (bottom) surgery: Penectomy, castration, vaginoplasty, clitoroplasty, vulvoplasty (plasty stands for the creation or the reconstruction of)

15.2.3 Non-breast, Nongenital Surgery

MtF transsexual patients treated with estrogens can realistically expect some degree of breast growth, some redistribution of body fat to approximate a female body appearance, decreased upper body strength, softening of the skin, decrease in body hair, and slowing or cessation of loss of scalp hair, but no feminization of facial features nor of the voice.

Beard density is also not significantly affected by cross-sex hormone administration. Removal of facial hair, via electrolysis or laser depilation, is a generally safe but costly and time-consuming process. However, in most cases, it greatly facilitates passing in the desired gender role.

A growing number of MtF transsexuals request non-breast, nongenital, feminizing surgical procedures to assist in their real-life experience. These mainly include liposuction of the waist, hair reconstruction surgery, antiaging operations, Adam's apple shaving, otoplasty or ear correction, and facial feminizing surgery. According to the SOC, none of these feminizing interventions require letters of recommendation from mental health professionals.

The two most common surgical interventions specifically performed in the MtF transsexual patient are facial feminizing surgery (FFS) and a reduction of the Adam's apple with possible voice surgery.

15.2.3.1 Facial Feminizing Surgery

In initial contacts, it is most often the face that provides the cues about the person, including gender. For the transsexual patient, nothing is more important than to appear externally congruent with the internal and emotional self.

Although the face, like most physical attributes, varies considerably in projection and form, there is an overlap of masculine and feminine forms and few remarkable differences between the two. Yet it is relatively easy to distinguish between female and male faces. Therefore, some basic attributes of what are commonly perceived to be masculine and feminine features have been set forth. These are the standards which facial surgery addresses, as part of an overall sex reassignment surgery.

The most frequently performed cosmetic surgical intervention includes (Hage, Becking, de Graaf, & Tuinzing, 1997):

- A correction of the typical male brow bossing, eventually combined with a contouring of the bone around the eyes and elevation of the brows through a standard forehead lift
- Cheek augmentation with an implant or with soft tissue filling
- A rhinoplasty to refine (mostly reduce) the contour, the width, the tip, and the tilt of the nose
- Modification of the chin with a small implant or through bony correction and repositioning
- Softening of the lower jaw contouring
- Various forms of hair reconstruction surgery

15.2.3.2 Chondrolaryngoplasty and Voice Surgery

Unlike hormonal therapy for the female-to-male patient, estrogen does not have any substantial or lasting influence on voice pitch, and speech therapy alone often does not produce satisfactory results. Even after transition, an individual may be identified as a man because of voice, and this occurs most often on the telephone. This can cause social and psychological problems. Surgical procedures to raise the patient's voice pitch ("crico-thyroidopexy" procedure) are performed with the aim of assisting social integration and can greatly improve self-esteem in some cases. In many patients, this procedure is combined with a reduction of the Adam's apple (Isshiki, 1989).

15.2.4 Breast Augmentation

Although genital reconstruction is the ultimate surgical request of the MtF transsexual patient, for many, breast augmentation (or breast "reconstruction") is equally important to increase subjective feelings of femininity. Mammoplasty provides a more feminine profile, facilitating adjustment. The presence of breasts significantly increases the factors involved in passability.

As mentioned previously, there are few changes that occur, even after years of estrogen therapy, that create a feminine appearance in the biologically male body. Hormonal therapy has no effect on voice, hand, feet, or shoulder dimensions, and while some breast formation occurs, for many, it is insufficient.

Mammogenesis in MtF transsexuals receiving estrogens follows a pattern similar to female pubertal mammogenesis, but it is not exclusively dose responsive, and about 2/3 to 3/4 of the male-to-female transsexuals do require an augmentation mammoplasty (Kanhai, Hage, Asscheman, & Mulder, 1999) because the preoperative condition of the breasts only responds to the softly pointed form seen in young girls or the small conical form seen in young adolescents.

Since, ultimately, breast prostheses are implanted in transsexuals with "young adolescent" breast development, the patient should be informed that the complex feminine form and age-related changes of the breast cannot be imitated by using symmetric round prostheses (Kanhai et al., 1999).

Other anatomical differences which should be taken into consideration in male-to-female transsexual patients are the larger width of the male breast, a stronger and a more developed muscle of the breast, and the smaller dimension of nipple and areola. Usually a 25 % larger volume of breast prostheses is chosen in MtF transsexuals compared to a breast augmentation in a biologically female patient, but even with a larger prosthesis, it is often impossible to avoid an abnormally wide cleavage between the breasts. The nipple and areola should always overlie the prosthesis centrally, and a position of these prostheses that is too much to the midline could result in extremely divergent nipples with an unacceptable appearance of the breast (Laub & Fisk, 1974).

Despite some sexual differences in chest wall and mammary anatomy, the implantation of mammary prostheses is not essentially different from breast augmentation in a biologically female patient, except that, usually, larger prostheses are used.

The same choices apply as to the kind of prostheses, the position of the pocket, the surgical approach, etc. (Monstrey et al., 2001).

The general complications of a breast augmentation are the same as in any surgical intervention: bleeding, infection, and/or delayed wound healing. However, these complications occur infrequently in augmentation mammoplasty. Complications specific to augmentation mammoplasty can include a decreased sensation in the nipple and/or part of the breast, capsular contraction (formation of dense scar tissue around the prosthesis), leakage of the content of the prostheses, and migration of the prostheses to an unnatural position.

In most institutions, breast augmentation is often performed during the same surgical procedure as the genital surgery. In this case, the operation starts with the breast augmentation, which is the most sterile part of the intervention. Both procedures, however, can even be carried out simultaneously if two surgical teams are available.

Recently, breast augmentation by the technique of lipofilling (fat injection) can be a valuable alternative to an augmentation with implants, especially in patients with enough subcutaneous fat who require only a limited increase in breast size.

Postoperative follow-up controls are mandatory in all patients undergoing breast augmentation. Several cases of breast cancer have been described in transsexuals after mammoplasty (Ganly & Taylor, 1995). The degree of risk may well be in proportion to the amount of hormones administered, but any person receiving feminizing hormonal therapy runs the same risk of breast cancer as does a genetic woman, and for both groups, family history of the disease is a risk factor. Additional investigation with mammography, ultrasound, or magnetic resonance can be indicated.

15.2.5 Genital Surgery

Karim, Hage, and Cuesta (1996) described the aim of genital reassignment surgery in male-to-female transsexual patients as follows:

> "*to create a perineo-genital complex as feminine in appearance and function as possible and free of poorly healed areas and painful scars. The urethra or urinary conduit should be shortened in such a way that the direction of the urinary stream is downward in the sitting position and it should be free of stenosis (narrowing) or fistulas (leakage). The neovagina should, ideally, be lined with moist, elastic and hairless. Its depth should be at least 10 cm and its diameter 30 mm. The sensation should be sufficient to provide satisfactory erogenous stimulus during sexual intercourse. Ideally, all these requirements should be met without overly-complex surgery, and addressing them should not create new lesions on other parts of the body.*"

Orchidectomy (castration), amputation of the penis, creation of the new vaginal cavity, the lining of this cavity, reconstruction of a urethral opening, and, finally, construction of the labia and clitoris are the major steps in every procedure.

Although the surgical techniques for vaginoplasty have evolved significantly, it must be stressed that both medical and surgical treatments are rarely perfect. Revisional surgery is sometimes required to optimize aesthetic results. Most patients require lubrication for sexual intercourse, and, of course, pregnancy is not possible.

Different methods exist for the lining of a newly reconstructed vagina: nongenital or penile skin grafts, penile-scrotal skin flaps, nongenital skin flaps, and reconstruction with a piece of bowel (Karim et al., 1996). However, the anteriorly pedicled penile skin flap inversion technique, as first performed by Dr. Burou (1973) in Casablanca, is still considered the technique of choice for vaginoplasty in male-to-female transsexuals. This penile skin flap is often combined with a (mostly) small

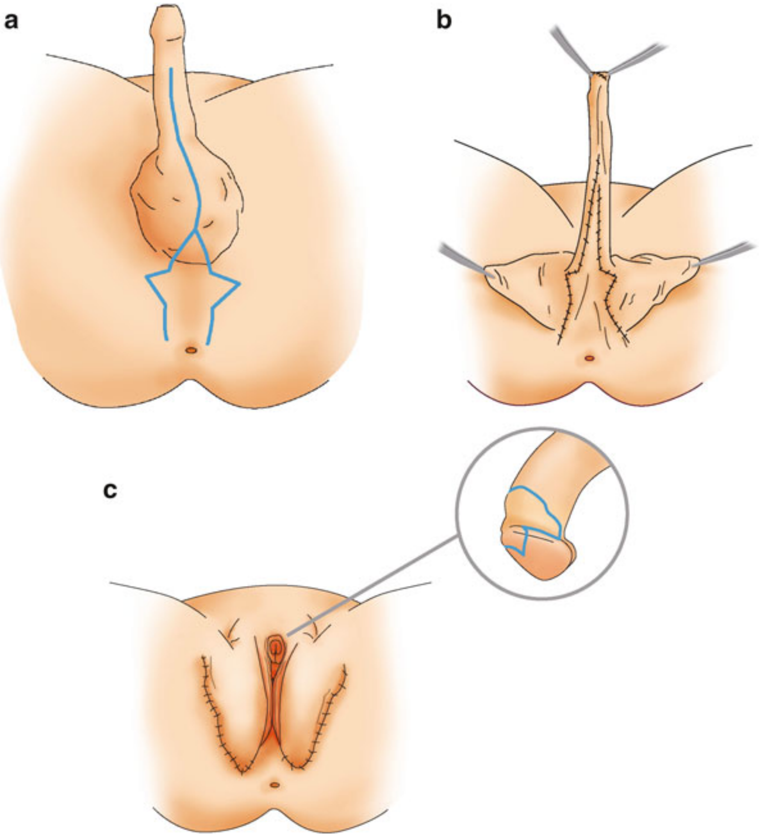

Fig. 15.1 (**a**–**c**) Vaginoplasty; penile inversion technique

dorsally based scrotal flap (see Fig. 15.1a, b, c) to widen the entrance of the vagina and to "break" the circular opening (Karim, Hage, Bouman, de Ruyter, & van Kesteren, 1995).

There are several advantages to penile skin flaps. They demonstrate less tendency to contract. In the event of inadvertent damage to the rectum, correction is easier, as it is immediately covered with vascularized tissue (Karim et al., 1995). Local innervation is provided and the flap is virtually hairless. Although pedicled flaps have much less tendency to contract than skin grafts, patients are still required to use a dilator postoperatively for 6 months.

Several refinements of the vaginoplasty using the inverted penile-scrotal skin flap technique have been described (Karim et al., 1995; Selvaggi et al., 2005). These include preoperative hair removal of the area at the base of the penis and posterior scrotum, preoperative bowel preparation, the use of a surgical drape with a rectal condom to guide the blunt dissection of the vaginal cavity, and the use of a double silicone vaginal stent to create and maintain a vaginal cavity of adequate dimension.

To consistently obtain a long and wide vagina, several authors recommend dissecting a wide and deep pocket during surgery. Additionally, they advise using a full-thickness graft (FTG) from the scrotum or abdomen if the amount of penile skin is insufficient to line the neovagina.

Finally, to produce a functional and aesthetic outcome, they advise near-complete resection of the corpus spongiosum, eversion of the urethral mucosa, and construction of the clitoral prepuce and labia minora. At present, most surgeons performing a clitoroplasty in transsexual patients use the dorsal portion of the glans penis with the dorsal neurovascular pedicle (Eldh, 1993; Giraldo et al., 2004; Hage & Kesteren, 1995). A novelty in the construction of the labia minora and, more specifically, the construction of a clitoral hood is to use the thin inner layer of penile foreskin which is harvested in continuity with the glans flap. It is only this way that the very delicate features of the anterior commissure of the vulva where the clitoris is located and where the labia minora start from the clitoral hood can be reconstructed in a naturally appearing way (Selvaggi et al., 2005).

The use of a pedicled intestinal transplant is only recommended in patients with an unsatisfactory previous vaginoplasty and with a short vaginal length and in the very young patients with a very small penis due to puberty halting hormones where it can be the first choice (and even the only technique) to obtain a vagina with adequate depth. The advantages of this technique are the length it provides, as well as a mucosal texture and natural lubrication. Disadvantages are the need for additional abdominal surgery and the possible long-term complications such as stasis of mucus, diversion or ulcerative colitis, and introital stenosis.

The normal postoperative course, when an anteriorly pedicled penile skin flap technique has been used in combination with a posterior scrotal flap, is the following.

The patient remains in bed for 4–5 days, with a dilator firmly in place to maintain the maximal dimensions of the vagina. Fractionized heparin is provided subcutaneously to prevent eventual thromboses. After 5 days, the dilator is removed, and the patient is allowed to ambulate. The neovaginal cavity is cleansed daily with an Iso-Betadine solution. The following day, the urethral catheter is removed. The patient is usually discharged on the seventh or eighth postoperative day and is instructed in the care of the neovagina.

The period of time that the dilator remains out is gradually increased over the following 3–6 months. Patients must know that dilation is a lifelong occurrence, but, if sexually active, the frequency can be greatly diminished.

Early postoperative complications include bleeding (usually resolved by applying some pressure), infection, or impaired wound healing. One specific complication related to the vaginoplasty procedure is a rectovaginal fistula (a connection between the rectum and the vagina), as the vaginal cavity needs to be created between the prostate urethra anteriorly and the rectum posteriorly. The rectum has a rather thin wall, and care must be taken to avoid a perforation. If this complication were to occur, a double-layer closure is performed, which usually heals without problem since a preoperative bowel prep is routinely performed.

Possible late complications include stenosis of the new urethral meatus.

15.3 Sex Reassignment Surgery in the Female-to-Male Transsexual

15.3.1 Overview

A complete list of gender reassignment surgery procedures in the female-to-male (FtM) transsexual can include:

1. *Non-breast, nongenital* surgery: Voice surgery (rare), liposuction, lipofilling, pectoral implants, and various cosmetic procedures.
2. *Breast* (top) surgery: Subcutaneous mastectomy (SCM).
3. *Genital* (bottom) surgery: Hysterectomy-ovariectomy, reconstruction of the fixed part of the urethra which can be combined with a metaidoioplasty (reconstruction of a micropenis) or with a phalloplasty (penile reconstruction) employing a pedicled (kept attached) or free vascularized flap (tissue transfer including microsurgical connection of blood vessels and nerves), vaginectomy (resection of the vagina), scrotoplasty (reconstruction of the scrotum), and implantation of erection and/or testicular prostheses.

In FtM transsexuals the operative procedures are usually performed in different stages: First is the subcutaneous mastectomy, which is often combined with a hysterectomy-ovariectomy. The next operative procedure consists of the genital transformation and includes a vaginectomy, a reconstruction of the horizontal part of the urethra, a scrotoplasty, and a penile reconstruction usually with a radial forearm flap (or an alternative). After about 1 year, penile (erection) prosthesis and testicular prostheses can be implanted when sensation has returned to the tip of the penis.

15.3.2 Subcutaneous Mastectomy

15.3.2.1 General Principles

Because hormonal treatment has little influence on breast size, the first (and, arguably, most important) surgery performed in the FtM transsexual is the creation of a male chest by means of a SCM. This procedure allows the patient to live more easily in the male role (Beer et al., 2001; Hage & Kesteren, 1995; Symmers, 1968) and thereby facilitates the “real-life experience,” a prerequisite for genital surgery.

The goal of the SCM in a FtM transsexual patient is to create an aesthetically pleasing male chest which includes removal of breast tissue and excess skin and reduction and proper positioning of the nipple and areola, while minimizing chest wall scars (Hage & Kesteren, 1995). Many different techniques have been described to achieve these goals, and in their large and well-documented series, Monstrey et al. (2008) described an algorithm of five different techniques to perform an aesthetically satisfactory SCM. Regardless of the technique, it is extremely important

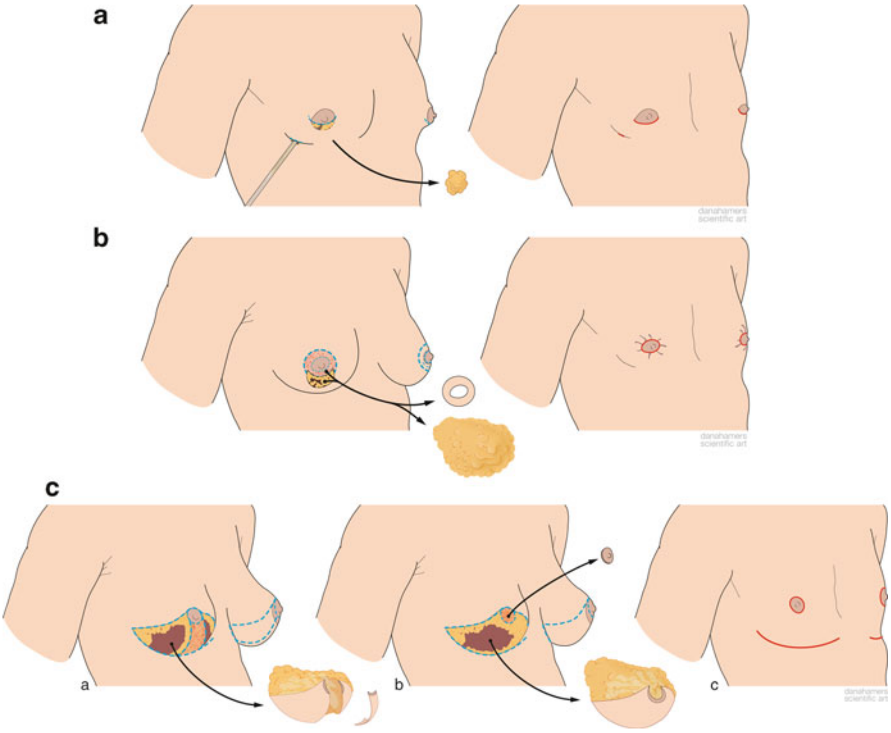
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Fig. 15.2 Subcutaneous mastectomy. (**a**) Semicircular technique, without skin resection. (**b**) Concentric circular technique. (**c**) Double-incision technique with pedicled nipple or free nipple graft. Illustrations by Dana Hamers Scientific Art. Figures are reprinted with permission from the copyright holders

to preserve all subcutaneous fat when dissecting the glandular tissue from the flaps. This ensures thick flaps that produce a pleasing contour. Liposuction is only occasionally indicated laterally or to attain complete symmetry at the end of the procedure.

15.3.2.2 Current Techniques

The *semicircular* technique is essentially the same procedure as that described by Webster in 1946 (Webster, 1946) for gynecomastia. A semicircular incision is made, usually around the lower side of the areola, to resect the glandular tissue. It is useful for individuals with smaller breasts and elastic skin. A sufficient amount of glandular tissue should be left beneath the nipple-areola complex in order to avoid a depression.

The particular advantage of this technique is the small and well-concealed scar which is confined to (the lower half of) the nipple-areola complex (see Fig. 15.2a).

In cases of smaller breasts with large prominent nipples, the *transareolar* technique is used. This allows for subtotal resection and immediate reduction of the nipple. The resulting scar traverses the areola horizontally and passes around the upper aspect of the nipple.

The *concentric circular* technique is used for breasts with a medium-sized skin envelope (B cup) or in the case of smaller breasts with poor skin elasticity. The double concentric incision enables the removal of a calculated amount of skin in the vertical or horizontal direction (Hage & Kesteren, 1995). A purse-string suture to reduce the diameter of the final circular scar is placed and set to the desired areolar diameter (usually 25–30 mm). The advantage of this technique is that it allows for reduction and/or repositioning of the areola and that the resulting scar will be confined to the circumference of the areola (see Fig. 15.2b).

The *extended concentric circular* technique is similar to the concentric circular technique but includes one or two additional triangular excisions of skin and subcutaneous tissue lateral and/or medial. This technique is useful for correcting skin excess and wrinkling produced by larger-sized breasts.

The *free nipple graft* technique has been proposed by several authors for patients with large and pendulous breasts (Cregten-Escobar, Bouman, Buncamper, & Mullender, 2012; Monstrey et al., 2001). It consists of harvesting the nipple-areola complex (NAC) as a full-thickness skin graft, amputating the breast, and grafting the NAC onto its new location on the chest wall. The advantages of the free nipple graft technique are easy chest contouring, excellent exposure, and more rapid resection of tissue, as well as nipple reduction, areola resizing, and repositioning (see Fig. 15.2cii). The disadvantages are the long residual scars, NAC pigmentation and sensory changes, and the possibility of incomplete graft take.

15.3.2.3 Complications

Postoperative complications are rather uncommon but can include hematoma (most frequent, despite drains and compression bandages), (partial) nipple necrosis, and abscess formation. This underscores the importance of achieving good hemostasis (control of bleeding) intraoperatively. Even in the patients without complications, about 25 % required an additional procedure to improve the aesthetic results. The likelihood of an additional aesthetic correction should be discussed with the patient in advance (Monstrey et al., 2001).

Finally, it is important to note that there have been reports of breast cancer after bilateral SCM in this population (Burcombe, Makris, Pittam, & Finer, 2003) since in most patients the preserved NAC and the always incomplete glandular resection leave behind tissue at risk of malignant transformation.

15.3.3 Phalloplasty

15.3.3.1 General Principles

In performing a phalloplasty for a FtM transsexual, the surgeon should reconstruct an aesthetically appealing neophallus, with erogenous and tactile sensation, which enables the patient to void while standing and to have sexual intercourse like a natural male, in a one-stage procedure (Gilbert et al., 1987; Hage, Bouman, de Graaf, & Bloem, 1993). The reconstructive procedure should also provide a normal scrotum, be predictably reproducible without functional loss in the donor area, and leave the patient with minimal scarring or disfigurement.

Despite the multitude of flaps that have been employed and described (often as case reports), the radial forearm flap, a free vascularized flap prelevated from the forearm and vascularized by the radial artery (see Fig. 15.3a), is universally considered the "gold standard" in penile reconstruction (Chang & Hwang, 1984; Gilbert et al., 1987; Hage et al., 1993; Hage & De Graaf, 1993; Sadove, Sengezer, McRobert, & Wells, 1993).

In the largest series to date (almost 300 patients), Monstrey et al. (2009) recently described the technical aspects of radial forearm phalloplasty and the extent to which this technique, in their hands, approximates the criteria for ideal penile reconstruction.

15.3.3.2 Technique

For the genitoperineal transformation (vaginectomy, urethral reconstruction, scrotoplasty, phalloplasty), two surgical teams operate at the same time: In the perineal area, the urologist performs a vaginectomy and lengthens the urethra with mucosa of the minor labia. The vaginectomy consists of a resection of the mucosa of the vagina. This reconstruction of the fixed part of the urethra is combined with a scrotal reconstruction by means of two transposition flaps of the greater labia resulting in a very natural looking bifid (with two parts) scrotum (see Fig. 15.3b, c).

Simultaneously, the plastic surgeon dissects the free vascularized flap of the forearm. The creation of a phallus with a tube-in-a-tube technique is performed with the flap still attached to the forearm by its vascular pedicle: The inner tube is for the urinary conduit; the outer tube is to give enough volume to the penis. A small skin flap and a skin graft are used to create a corona (border) that simulates the glans of the penis.

Once the urethra is lengthened and the acceptor vessels are dissected, the free flap can be transferred to the pubic area where first the urethral anastomosis is connected. Thereafter, the radial artery is microsurgically connected to the common femoral urethra in an end-to-side fashion, and the venous anastomosis is performed between the cephalic vein and the greater saphenous vein. One forearm nerve is connected to the ilioinguinal nerve for protective sensation, and the other nerve of

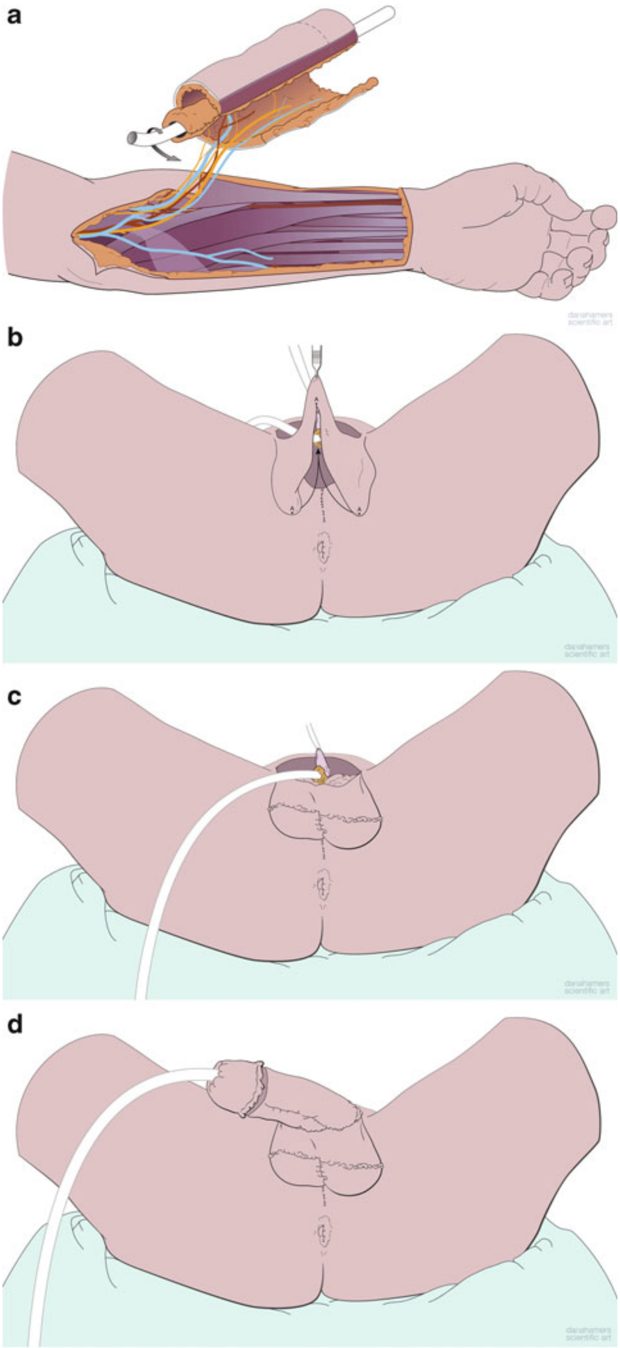
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Fig. 15.3 (**a**) The radial forearm flap, the "gold standard" in penile reconstruction. (**b** and **c**) Scrotal reconstruction by means of two transposition flaps of the greater labia. (**d**) Radial forearm flap phalloplasty. Illustrations by Dana Hamers Scientific Art. Figures are reprinted with permission from the copyright holders the arm is anastomosed to one of the dorsal clitoral nerves for erogenous sensation. The clitoris is buried underneath the penis, thus keeping the possibility to be stimulated during sexual intercourse with the neophallus. All patients receive a suprapubic urinary diversion postoperatively. The patients remain in bed during a 1-week postoperative period, after which the transurethral catheter is removed and voiding has begun. The average hospital stay for the phalloplasty procedure is two and a half weeks.

Tattooing of the glans could be performed after a 2–3-month period, before sensation returned to the penis. Implantation of the testicular and erection prostheses is undertaken typically after 1 year when sensation has returned to the top of the penis.

15.3.3.3 The Ideal Goals of Penile Reconstruction

What can be achieved with this radial forearm flap technique as to the ideal requisites for penile reconstruction (Monstrey et al., 2009)?

1. *Is It a One-Stage Procedure?*
   Already a long time ago, Hage and De Graaf (1993) stated that a complete penile reconstruction with an erection prosthesis never can be performed in one single operation. Nowadays, most GRS surgeons perform the SCM first and most often in combination with a total hysterectomy and ovariectomy. Erection prostheses are implanted only after 1 year.
2. *Is the Phallus Aesthetic?*
   The aesthetic advantages of the radial forearm flap include the following: The flap is thin and pliable allowing the construction of a normal-sized, tube-in-a-tube penis; the flap is easy to dissect and is predictably well vascularized, making it safe to perform an (aesthetic) glans-plasty at the distal end of the flap. The final cosmetic outcome of a radial forearm phalloplasty (see Fig. 15.3d) is a subjective determination, but the ability of most patients to shower with other men or to go to the sauna is the usual cosmetic barometer.
3. *With Tactile and Erogenous Sensation?*
   Of the various flaps used for penile reconstruction, the radial forearm flap has the greatest sensitivity.

   Selvaggi, Monstrey, Ceulemans, et al. (2007) always connect one forearm nerve to the ilioinguinal nerve for protective sensation and the other forearm nerve with one dorsal clitoral nerve. The denuded (skin removed) clitoris was always placed directly below the reconstructed penis. Later manipulation of the neophallus allowed for stimulation of the still-innervated clitoris. After 1 year, all patients had regained tactile sensitivity in their penis, which is an absolute requirement for protection and safe insertion of an erection prosthesis (Selvaggi, Monstrey, Ceulemans, et al., 2007; Selvaggi, Monstrey, Hoebeke, et al., 2007).

   In a long-term follow-up study on postoperative sexual and physical health, more than 80 % of the patients reported improvement in sexual satisfaction and greater ease in reaching orgasm (100 % in practicing postoperative FtM transsexuals) (De Cuypere et al., 2005).

4. *Could the Patients Void While Standing?*
   For FtM transsexuals undergoing a phalloplasty, the ability to void while standing is a high priority (Selvaggi, Monstrey, Ceulemans, et al., 2007). Unfortunately, the reported incidences of urological complications, such as urethrocutaneous fistulas (leakage), stenosis and strictures (narrowing of urethral tube), and hair growth within the urethra, are extremely high in all series of phalloplasties, even up to 80 %. In their series of radial forearm phalloplasties, Hoebeke et al. (2005) still reported a urological complication rate of 41 %, but the majority of these early fistulas closed spontaneously, and ultimately *all* patients were able to void through the newly reconstructed penis.
5. *With Minimal Morbidity?*
   Complications following phalloplasty include the general complications attendant to any surgical intervention and, more specifically, the already mentioned fistulas and/or stenosis. Other complications are related to the free tissue transfer. The total flap failure in the series of Monstrey et al. (2009) was very low (<1 %), despite a somewhat higher anastomotic revision rate (12 %). About 7 % of the patients demonstrated some degree of skin slough or partial flap necrosis. This was more often the case in smokers, in those who insisted on a large-sized penis requiring a larger flap, and also in patients having undergone anastomotic revision.
6. *No Functional Loss and Minimal Scarring in the Donor Area*
   The major drawback of the radial forearm flap has always been the unattractive donor site scar on the forearm. However, Selvaggi, Monstrey, Hoebeke, et al. (2007) conducted a long-term follow-up study of 125 radial forearm phalloplasties and did not find any major or long-term functional and surprisingly limited aesthetic impairment after harvesting such a large forearm flap.
7. *Normal Scrotum?*
   For the female-to-male patient, the goal of creating natural-appearing genitals also applies to the scrotum. The novel scrotoplasty technique described by Selvaggi et al. combines an advancement with an anterior rotation of labial skin and the excellent aesthetic outcomes of this male-looking (anteriorly located) scrotum; the functional advantage of fewer urological complications and the easier implantation of testicular prostheses make this the technique of choice (Hoebeke, De Cuypere, Ceulemans, & Monstrey, 2003).
8. *Allowing Sexual Intercourse?*
   In a radial forearm phalloplasty, the insertion of erection prosthesis is required in order to engage in sexual intercourse. A major concern regarding erectile prostheses is the long-term results of these devices showing high complication rates (Hoebeke et al., 2005).

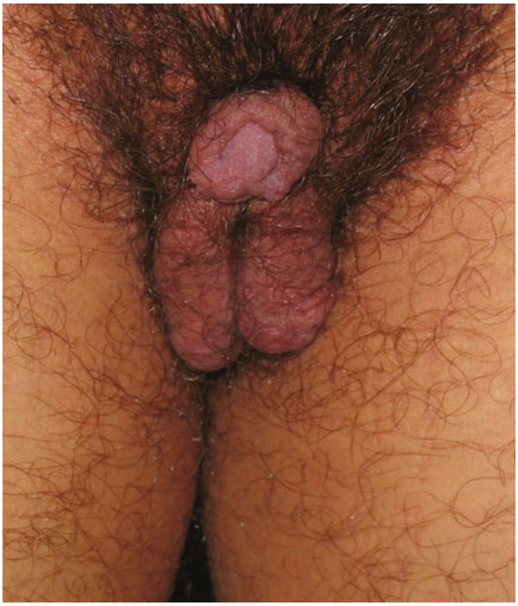

Fig. 15.4 Metaidoioplasty

15.3.3.4 Alternative Phalloplasty Techniques

1. *Metaidoioplasty*
   A metaidoioplasty uses the (hypertrophied) clitoris to reconstruct a microphallus in combination with a lengthening of the urethra. FtM patients interested in this procedure should be informed preoperatively that voiding while standing cannot be guaranteed and that sexual intercourse will not be possible (see Fig. 15.4).
   The major advantages of metaidoioplasty include the complete lack of scarring outside the genital area and the substantially lower costs. Complications of this procedure also include urethral obstruction and/or urethral fistula.
2. *Fibula Flap*
   There have been several reports on penile reconstruction with the fibular flap of the lower leg which includes a piece of bone and is based on the peroneal artery and vein. The advantage of the fibular flap is that it makes sexual intercourse possible without a penile prosthesis. The disadvantages are a pointed deformity to the distal part of the penis when the extra skin can glide around the end of fibular bone and that a permanently erected phallus is impractical.

   Many authors seem to agree that the fibular osteocutaneous flap is an optimal solution for penile reconstruction in a natal male (Sengezer, Ozturk, Deveci, & Odabasi, 2004), e.g., after trauma or oncological resection.
3. *New Surgical Developments: The Perforator Flaps*
   Perforator flaps (flaps based on small blood vessels only) are considered the ultimate form of tissue transfer. Donor site morbidity is reduced to an absolute

minimum, and the usually large vascular pedicles provide an additional range of motion or an easier vascular anastomosis. At present, the most promising perforator flap for penile reconstruction is the pedicled anterolateral thigh (ALT) flap which could be an attractive alternative to the radial forearm phalloplasty. The donor site is less conspicuous, and secondary corrections at that site are easier to make. The disadvantages of this flap are the usually excessive thickness of the flap in these biologically female patients and the additional difficulty reconstructing a penile urethra since a tube-in-a-tube technique is rarely possible because of the fact that the subcutaneous fatty layer is too thick.

Composite tissue allograft (CTA) or transplantation of a penis from a donor is not really considered as a surgical option to date because of the lack of a “vital” indication and because of the burden of immunodepressive therapy.

15.4 Conclusion: The Importance of a Multidisciplinary Approach

Gender reassignment, particularly reassignment surgery, requires close cooperation between the different surgical specialties. Therefore, professionals who unite for the purpose of creating a gender reassignment program should be aware of the necessity of a strong alliance between the plastic surgeon, the urologist, and the gynecologist. In turn, the surgeons must commit to the extended care of this unique population which, by definition, will protract well into the future.

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Chapter 16
The Impact of Stigma on Transgender Identity Development and Mental Health

Walter Bockting

Abstract The existence of transgender and gender-nonconforming people has been documented throughout history and across cultures. In the twentieth century, transgender expression became medicalized and sex reassignment became available, initially enforcing a binary understanding of sex/gender as either male or female, man or woman, and masculine or feminine. The goal was to adjust and live either as a man or as a woman, evading the social stigma attached to gender nonconformity. However, it quickly became clear that stigma was pervasive and continued, even for those who fully transitioned to living as a member of the other sex. Transsexual and transgender individuals found support among each other, affirmed their specific identity and experience, and advocated for their rights. Since the 1990s, the paradigm shifted toward (re)discovery of a spectrum of gender diversity. Transgender is now an identity, no longer a disorder, and identifying as such is for many an important part of their coming-out process to affirm their differentness, find belonging in a community of peers, challenge stigma, and advocate for inclusion, respect, and acceptance. Research has established the association between discrimination and psychological distress, with family support, identity pride, and particularly peer support serving as protective factors. What is needed is a greater understanding of the mechanism of stigma, both for the minority population and for the sociocultural context in which stigma is produced and perpetuated, to inform policies promoting transgender rights and resilience.

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16.1 Historical Background: From Gender Nonconformity to Sex Change

The existence of gender-nonconforming and transgender people has been documented throughout history and across cultures (Bullough & Bullough, 1993; Feinberg, 1996). Examples of such gender diversity include “two-spirit” individuals in Native American tribes (Roscoe, 1991; Williams, 1986), “acault” in Myanmar (Coleman, Colgan, & Gooren, 1992), “maa khii” in Thailand (Taywadietep, Coleman, & Domronggittigule, 1997), “travesti” in Brazil (Kulick, 1998), and “hijras” in India (Nanda, 1999). In the Netherlands, Dekker and van de Pol (1989) reported more than a hundred cases of female cross-dressing (females dressing as men) in the seventeenth and eighteenth centuries. While motivations for cross-dressing and living as man varied (e.g., economic, psychological, sexual, taking on roles only acceptable for men), experiences of stigma (e.g., fear of discovery, negative social reactions) were common across this group despite the popularity of cross-dressing and crossgender behavior in art and folklore. In the nineteenth century, however, cases of female cross-dressing declined markedly, attributed to increased societal barriers (e.g., enforced military service, civil registration, medical exams). The authors concluded that female cross-dressing and living in the male gender role were perceived as threatening the hierarchy between the sexes and that gender ambiguity seemed to put people ill at ease.

In the early twentieth century, when males who cross-dressed faced legal arrest, Hirschfeld (1910/1991) advocated for them by medicalizing transgender expression. He argued that instead of criminalizing cross-dressing and crossgender behavior, people needed to be compassionate as he believed the behavior involved an innate orientation. In the second half of the twentieth century, after behavioral therapies aimed at changing gender identity/expression to become congruent with sex assigned at birth had failed, advances in medical technology were applied to attempt to achieve the opposite: to change an individual’s primary and secondary sex characteristics to become congruent with their perceived gender identity (Benjamin, 1966; Green & Money, 1969; Hastings, 1974). Indeed, this approach of sex reassignment became known in the popular vernacular as “sex change” (Meyerowitz, 2002). While Benjamin (1966) acknowledged a spectrum of transvestism and transsexualism, much of the focus shifted toward selecting appropriate candidates for hormone therapy and surgery who could successfully “pass” and assimilate as members of the “opposite” sex. The aim was to alleviate their suffering by facilitating a change in sex while minimizing the risk of regret of undergoing irreversible medical intervention (Hastings, 1969; 1974; Hastings & Markland, 1978).

Also in the Netherlands, sex reassignment became available coordinated by the *Stichting Nederlands Gender Centrum* (de Vaal, 1971; Verschoor, 1986). The VU University Medical Center (VUmc) provided hormone therapy and surgery (Gooren, Asscheman, & Megens 1986). Post hoc follow-up research supported the value of sex reassignment in alleviating gender dysphoria: The vast majority of transsexual individuals who received hormone therapy and had sex reassignment surgery reported satisfaction (Kuiper, 1991), and reports of regrets were extremely rare (Kuiper & Cohen-Kettenis, 1998). The VUmc became an international leader in patient-oriented research reporting on the long-term effects of hormone therapy in a large cohort of transsexual adults (e.g., van Kesteren, Asscheman, Megens, & Gooren, 2003). Initiated in collaboration with Utrecht University, the Dutch also pioneered early medical intervention in the form of puberty-delaying hormones followed by cross-sex hormone therapy (Cohen-Kettenis & van Goozen, 1998; Delemarre-van de Waal & Cohen-Kettenis, 2006), which has now become an approach applied worldwide (Coleman et al., 2012). Moreover, research at the Netherlands Institute for Brain Research showed that an area of the hypothalamus of the brain of transsexual women was more similar to that of nontransgender women than to that of men (Kruijver et al., 2000; Zhou, Hoffman, Gooren, & Swaab, 1995). At the height of the sex change paradigm in the Netherlands, some argued for replacing the term "sex reassignment" with *detransseksualisatie* (detranssexualization) to affirm transsexual (or, rather, "transsexed") individuals' lifelong core crossgender identity and the success of the available treatment to fulfill their need to live as members of the "opposite" sex (Kuiper, 1991; Verschoor, 1986).

16.2 Social Stigma: From *Detransseksualisatie* to Transgender Coming Out

Since the 1990s, first in the USA and subsequently also in Western Europe, the paradigm shifted from seeing gender identity as binary (either boy/man or girl/woman) toward (re)discovery of a spectrum of gender diversity. As a generation of sex-reassigned transsexuals came of age, recognition grew of a transsexual or transgender identity "outside the boundaries of gender, beyond the constructed oppositional nodes" of male versus female (Stone, 1991, p. 295). Transsexual and transgender individuals began to affirm their identity as distinct from nontransgender women and men, honoring their specific experience and roots (e.g., Bornstein, 1994). This change in paradigm can be understood in the context of social stigma. As Pfäfflin (2011; see Chap. 17) argued, identity becomes relevant when it is no longer assumed but questioned, when we are dealing with a deficit. Thus, the social stigma attached to gender nonconformity (deficit) created the need to "come out" and affirm an identity that transcends the gender binary.

In the transgender coming-out process, support from similar others plays a critical role (Bockting & Coleman, 2007). According to Erikson (1956), identity development is an interactive, social process during which an individual learns to experience himself or herself as unique and continuous across time and situations (personal identity), while at the same time belonging to a social group (group identity). During the sex change paradigm of the 1960s and 1970s, "true transsexual" candidates for sex reassignment were to find a sense of belonging among nontransgender women and men. However, "transvestites," whose crossgender identification was considered incomplete or ambiguous (Benjamin, 1966), sought and found each other. In the USA, Virginia Prince founded the peer support organization Tri-Ess: the Society for the Second Self. Virginia eventually lived full time in the female gender role yet was vocal about not having had genital reconstructive surgery. She popularized the term "transgender" as an alternative to "transsexual" and "transvestite" to signify an identity that transcended the gender binary and was continuous. Meanwhile, participants in the Gender Identity Project in New York City proposed to spell "tran*s*exual" with one "s" to signify an ongoing identity beyond the transition phase and challenged the shame associated with the pressure to pass as non-transgender in favor of affirming their specific shared identity and experience (Warren, 1993). The following quote illustrates this transformative change:

> "*Often we want to pass as non-transexuals because of an unexpressed conviction that only non-transexual women define femaleness … I used to say, 'Well sometimes I still sound like a man.' And then it occurred to me. I don't sound like a man. I sound just exactly and precisely like a transexual woman … I used to feel embarrassed because I had 'man's hands or a 'man's build.' But I don't. I have the hands and build of a transexual woman. I stopped defining myself in terms of other people's categories and started defining myself in terms of me*" (Warren, 1993, p. 16).

In the Netherlands, the *Nederlandse Vereniging voor Seksuele Hervorming* (NVSH) had long organized peer support through its *Travestie & Transseksualiteit (T&T)* network, followed by such support organizations as *Het Jongensuur*, *Stichting Rene(e)*, *Humanitas*, *Transvisie*, and *Transgender Netwerk Nederland*.

Gradually, as transsexual and transgender individuals built community and gained visibility, the term transgender evolved into an umbrella term blurring the clear distinction between transvestites and transsexuals, allowing for the recognition of a wide spectrum of gender diversity (Bockting, 1999; De Jong, 1999). Changes in gender role, hormone therapy, and surgery were no longer considered three steps in a linear process of sex reassignment but rather three options that individuals may utilize to varying degrees to actualize their particular transgender identity (Bockting, 2008). Finally, genderqueer emerged as a term especially popular among the younger generation to affirm their transgression from the gender binary (Bockting, 2008; Harrison, Grant, & Herman, 2012). Recently, however, some transsexual activists have argued that they do not experience their gender identity as variant but rather as completely on the other end of the gender spectrum, reaffirming the term "transsexual" to distinguish themselves from gender-variant and gender-nonconforming individuals. To be inclusive of both transgender- and transsexual-identified individuals, the short form "trans" is now often used.

Thus, in the context of social stigma, transgender identities emerge to affirm gender nonconformity and empower transgender people to develop resilience. This process is similar to the coming-out process of gay and lesbian individuals (see Bockting & Coleman, 2007), and it is therefore not surprising that the transgender (T) community established a strong coalition with the lesbian, gay, and bisexual (LGB) community in the shared concern and fight against stigma, which for LGB individuals also often centers around gender role nonconformity. While gender identity and sexual orientation are distinct components of one's sexual identity, nonconformity to what Butler (1991) called “the heterosexual matrix” creates common ground for LGBT people to affirm their identity and experience within a community of similar others, a process of empowerment (Bockting, Rosser, & Coleman, 1999), resilience (Bockting, Miner, Swinburne Romine, & Coleman, 2013), or minority stress coping (Meyer, 2003).

16.3 Minority Stress, Mental Health, and Resilience

Transsexual and transgender individuals face persistent and intense stigma. For example, in a national study of the US transgender population, 70 % reported verbal abuse and harassment related to being transgender and 38 % reported employment discrimination (Bockting et al., 2013). In a recent national survey in the Netherlands, 42 % reported having received negative reactions because of their transgender identity, most commonly in public (38 %) and at work or school (21 %) (Keuzenkamp, 2012). The minority stress model (Meyer, 2003) postulates that stigma attached to one’s minority status creates added stress beyond general stress that individuals from both the majority and minority populations face. This added stress then is expected to negatively affect mental health and other health outcomes. However, minority stress-coping processes or resiliency factors may ameliorate the negative impact of stigma on mental health. Minority stress-coping processes can operate on an individual or community level and include personal acceptance and integration of minority identity; peer support, community solidarity, and cohesiveness; and family support (Meyer, 2003). A community of peers not only provides a space where one is not stigmatized by others but also provides an alternative reference group to evaluate oneself in comparison to similar others rather than with members of the majority population.

The minority stress model has been tested with LGB populations, leading to greater understanding of the LGB population’s vulnerability to mental health concerns (e.g., Lehavot & Simoni, 2011; Lewis, Derlega, Brown, Rose, & Henson, 2009; Meyer, 1995). However, until recently, this model had not been tested with the transgender population. Five recent quantitative studies established the negative association between stigma and mental health among the transgender population in North America. Discrimination related to being transgender was identified as an independent predictor of suicide among transgender women and men in San Francisco (Clements-Nolle, Marx, & Katz, 2006). Also in San Francisco, among transgender women with a history of sex work, discrimination and the need for social support were positively associated with depression (Nemoto, Bödeker, & Iwamoto, 2011). Among transgender women in New York City, gender-related abuse was strongly associated with depression during early stages of life but, especially for the younger generation, declined during later stages of life, attributed to the development of moderately effective coping mechanisms (Nuttbrock et al., 2010). Among a sample of the transgender population recruited via respondent-driven sampling in Ontario, Canada, rates of depression were high (61 % for transgender women and 66 % for transgender men), and depression was associated with transgender-related stigma and discrimination (Rotondi, Bauer, Scanlon et al., 2011; Rotondi, Bauer, Travers et al., 2011). Finally, three factors of resilience (identity pride, family support, and transgender peer support) were tested in a large Internet-based sample of the US transgender population (Bockting et al., 2013). Using a standardized instrument, 49 % of transgender women and 37 % of transgender men reported clinical levels of depression; 33 % of each gender group reported clinical levels of anxiety. Both enacted stigma (actual experiences of discrimination) and felt stigma (stigma consciousness, anticipated or perceived rejection) were positively associated with overall psychological distress. While self-acceptance and a sense of pride in being transgender as well as support from family were both negatively associated with psychological distress (i.e., the more pride and support, the less psychological distress), support from transgender peers was the only protective factor to moderate and thus buffer the negative impact of stigma on mental health.

16.4 Stigma and Transgender Identity Development

As argued above, affirmation of a transgender identity becomes especially salient in the context of social stigma attached to gender nonconformity. The transgender population is diverse and many attempts have been made to categorize gender-variant individuals, and especially when it comes to transgender women, a number of typologies have been proposed (see Bockting, in press, for an overview). Notwithstanding differences between the various typologies, a common understanding is that there are two groups of transsexual women: one group with an onset of crossgender feelings and identity in childhood and another group with an onset in adolescence or adulthood (Nieder et al., 2011). These two groups have been found to differ in sexual orientation and mental health (Lawrence, 2010). When we consider the role of stigma in transgender identity development, the difference of nonconformity in gender *role* between the two groups becomes salient.

Children who are visibly gender role nonconforming in childhood have no choice but to learn to cope with the attached enacted stigma at an early age. Their coming-out process is accelerated. Stigma and rejection at an early age put these gender-nonconforming youth at risk for isolation, academic performance issues and school dropout, homelessness, substance abuse, and suicide (Garofalo, Deleon, Osmer, Doll, & Harper, 2006; Grossman and D'Augelli 2007; Sausa, 2005; Wyss, 2004). However, it also provides the opportunity to develop early resilience. Due to visible gender role nonconformity, their gender identity is noticed and accurately mirrored, aiding in the development of a coherent sense of self, albeit a nonconforming self. In contrast, those who are not visibly gender role nonconforming in childhood are able to hide and suppress their crossgender feelings. Their gender identity is not noticed, and what is mirrored is the gender identity they maintain to the outside world in accordance with what is expected of them. Their coming out is delayed. Felt stigma and shame puts these youth at risk for developing obsessive/compulsive features of cross-dressing and gender dysphoria and may result in leading a double life that takes its toll on their mental health. Thus, stigma affects the identity development of gender-*role*-conforming and gender-*role*-nonconforming children and adolescents differently, with profound impact on their human development and mental health.

Grounded in interactionist (Erikson, 1956; Plummer, 1975) and interpersonal theory (Sullivan, 1953) and informed by extensive clinical experience, a stage model of gay and lesbian identity development was adapted to transgender identity development (Bockting & Coleman, 2007). In the first phase, *Pre-Coming Out*, transgender feelings are present yet have not been named as such. Rather, there is a growing awareness of being different, with accompanying shame and alienation from others. The developmental task of this stage is to face this differentness and begin to move toward the second stage, *Coming Out*, by acknowledging transgender feelings to self and others. The developmental task of this second stage is to resolve any confusion about transgender feelings and achieve self-acceptance. The response of others is critical, especially in the beginning. Positive reactions can lessen shame and reduce isolation, while negative reactions reinforce it, delay further coming out, and increase vulnerability to self-harm and suicide. Therefore, taking calculated risks by first disclosing to those who are most likely to be accepting is recommended. But even then, immediate acceptance may not be realistic; support from others (counselor or transgender peers) can be instrumental in putting reactions from others in perspective.

The third stage, *Exploration*, is the time to learn as much as possible about being transgender through immersion in available resources and the community, both online and off-line. The first developmental task of this stage is experimentation to find a comfortable gender role and expression. This may include the pursuit of hormone therapy and/or surgery. The second developmental task is to achieve a sense of personal attractiveness and sexual competence, which for some includes a second adolescence. Completion of this stage involves transforming shame into pride and working through any internalized transphobia, often through participation in community organizing and activism.

In the fourth stage, *Intimacy*, the focus shifts from the relationship with oneself to fulfilling the desire for close relationships with others. The developmental tasks of establishing and maintaining intimate relationships may be complicated by a history of anxious attachments. It may be further complicated by the impact of stigma on partners, who, for example, may hesitate to introduce a transgender partner to their family. However, with practice and perseverance, these challenges can be overcome; many transgender individuals report being in committed relationships (Bockting, Benner, & Coleman, 2009; Iantaffi & Bockting, 2011; Lawrence, 2005). Finally, in the fifth stage, *Integration*, being transgender becomes an integral part of a person's overall identity. The developmental task of this stage is to come to a deeper level of self-acceptance and appreciate the added value of being transgender. Having found a comfortable gender role expressed in relationship with others, identity labels become less important and there is room for greater ambiguity. If questions arise around one's gender identity, these questions can be addressed with confidence. There is a shift in focus to pursue other life goals and aspirations. This may also be a time of giving back to the community and/or taking on leadership roles in society more generally.

16.5 Implications for Clinical Practice and Advocacy

Clinicians can play an invaluable role in facilitating identity development, promoting the health and mental health, and improving the quality of life of transgender individuals and their families. While hormone therapy and/or surgery are medically necessary for many transsexual and transgender individuals, finding a comfortable gender role and expression is in large part a psychosocial process. Moreover, growing up with a stigmatized identity poses challenges for human development that may take its toll on mental health. Mental health professionals can help in at least four important ways: (1) assess and treat the negative effects of stigma on mental health, (2) facilitate identity development, (3) foster resilience in coping with ongoing stigma, and (4) engage in advocacy to combat social stigma.

The Standards of Care for the health of transsexual, transgender, and gender-nonconforming people (Coleman et al., 2012) guide health professionals in providing transgender-specific health care. It includes guidelines for mental health professionals. While a psychological evaluation is no longer an absolute requirement in the Standards of Care for access to hormone therapy, referral for such an evaluation is recommended, particularly when a mental health screen identifies significant mental health concerns. Treatment of depression and other mental health conditions can greatly facilitate completion of the developmental tasks of the coming-out process (Bockting & Coleman, 2007; Bockting, Knudson, & Goldberg, 2006; Fraser, 2009). Fostering family support, identity pride, and particularly peer support will offer protection. In addition, teaching specific stigma-management skills (e.g., putting reactions of others in perspective, assertiveness, personal advocacy, problem solving, rallying support) can empower transgender individuals and their families to improve the capacity of their community to respect, accommodate, and accept them. Finally, health professionals can engage in advocacy on a family, community, and society level to fight stigma and create an environment in which transsexual and transgender people can thrive and gender diversity is celebrated. For example, health professionals can educate and provide resources for families with a transgender loved one, facilitate gender role transitions in the workplace, educate the courts through expert witness testimony during civil cases, and advocate for transgender inclusion in human rights protection legislation.

16.6 Directions for Future Research

In recent years, advocacy efforts for transgender rights around the world have continued to grow. LGBT organizations are finally taking the “T” seriously and are putting their weight, leverage, and resources behind transgender causes. In addition, community organizations specifically dedicated to the needs of the transgender population are making new advances by using a human rights framework (i.e., the right to universal health care for all) to promote the health and well-being of transsexual, transgender, and gender-nonconforming individuals and their families. To support these positive developments and to facilitate further progress, research to inform evidence-based policy decisions is urgently needed. For example, research on the effects of gender affirmation on the mental health and psychosocial adjustment of transgender youth or on the cost-effectiveness of transgender-specific health care (including surgery) could inform policy that ensures greater access to care.

In the period 1960–1990, research in transgender health was mostly clinical, patient-oriented research (Institute of Medicine, 2011). Since the 1990s, a public health approach to transgender health research emerged, largely spurred by the impact of the HIV epidemic on the transgender population (e.g., Bockting & Avery, 2005). This body of research indicated that HIV was highly prevalent among subgroups of the population that face multiple, compounding challenges—many driven by social stigma—such as poverty, discrimination and violence, depression and suicide, and lack of access to culturally and clinically competent general as well as transgender-specific health care (Lombardi., 2010). Thus, while HIV remains a major concern among the transgender population, other stigma-related health issues need investigation. Health inequities in some of these other areas are beginning to be documented (e.g., Bockting et al., 2013; Rotondi, Bauer, Scanlon et al., 2011; Rotondi, Bauer, Travers et al., 2011), despite the methodological challenges of epidemiological research with a geographically dispersed, relatively small, and "hidden" population, for which a sampling frame to draw a representative sample remains unavailable.

What is needed next are longitudinal cohort studies of diverse segments of the transgender population to examine the *processes* of stigma, minority stress, health, and resilience. A greater understanding of effective coping with stigma can inform the development of evidence-based prevention strategies. What is also needed are studies that advance our understanding of the *mechanism* by which stigma negatively impacts mental health and other health outcomes and the development and evaluation of corresponding intervention strategies (e.g., Hatzenbuehler, 2009; Hatzenbuehler, Nolen-Hoeksema, & Dovidio, 2009). Finally, research that increases our understanding of gender-related stigma on an individual, group, community, and society level is needed to guide interventions to reduce ignorance among majority populations and policy makers and to enhance successful integration of transsexual, transgender, and gender-nonconforming people into society.

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Chapter 17
Identity: A Historical and Political Reflection

Friedemann Pfäfflin

Abstract In the 5th edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-5, American Psychiatric Association 2013), published by the American Psychiatric Association in May 2013, the former diagnosis "Gender Identity Disorder" (DSM-IV, American Psychiatric Association 1994) was replaced by the diagnosis "Gender Dysphoria." Prior to the diagnosis "Gender Identity Disorder," the respective diagnosis in the DSM was "Transsexualism," for the first time included in the DSM-III (American Psychiatric Association 1980) and still used in the International Classification of Diseases (ICD-10, World Health Organization 1992).

In the course of the process of revising DSM-IV and preparing DSM-5 and in the still ongoing course of the revision of the International Classification of Diseases (from ICD-10 to ICD-11), all three diagnoses were challenged by many authors arguing that neither transsexualism nor various forms of gender identity and gender expression qualified as psychiatric disorders and that their inclusion automatically contributes to the discrimination of gender-variant individuals.

This chapter reflects on the history of the terms identity in general and especially on the terms sexual and/or gender identity as well as political implications of their use in the context of psychiatric diagnoses.

17.1 Introduction

Peggy Cohen-Kettenis chaired the sub-work group of the American Psychiatric Association in charge of preparing the revision of the diagnosis "Gender Identity Disorders," used in DSM-IV (1994), for the new DSM-5 edition (American

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Psychiatric Association, 2012). The other members of the sub-work group were Jack Drescher, New York; Heino Meyer-Bahlburg, New York; Bill Womack, Seattle; Ken Zucker, Toronto; and the author. In spring 2010, from February, 10, 2010, to April, 20, 2010, the American Psychiatric Association published the new diagnoses and criteria proposed by the individual work groups on its web page and invited comments. During this period, many thousands of written comments were received, which were very unevenly distributed among the diverse diagnosis groups. For the *Sexual and Gender Identity Disorders* (including the diagnoses *Sexual Dysfunctions* and *Paraphilia*) work group alone, there were more than 6,000 comments, ranking them third in being the most numerous. This shows how closely the proposed revisions were monitored by the public.

The majority of comments about gender identity disorders called for complete removal of this diagnosis from the DSM-5. They referred especially to the fact that gender identity in each of its variations is something useful and therefore would not fall within the area of psychiatry. As with homosexuality, which also used to be listed as a DSM and ICD diagnosis, it would amount to discrimination if the diagnosis of gender identity disorder were to be retained in DSM-5.

Bearing in mind that health insurance is not responsible for phenomena for which there is no diagnosis and thus need not reimburse treatment costs associated with these phenomena, another considerable number of comments demanded that gender identity disorders should be classified as a physical condition in order to at least secure health insurance coverage of hormonal and surgical procedures for transsexuals. The DSM is, however, primarily a psychiatric classification and, contrary to the ICD-10, is not complemented by a catalogue of all other diseases and disorders. Additionally, there are no scientifically validated physical causes for these phenomena in order to justify their assignment to the physical syndromes.

The discussion about whether to either retain or remove gender identity disorders was and is being conducted with great intensity and to some extent polemically, which indicates that we are not dealing with a purely academic issue. It has quite obviously to do with identity. That there was such a diagnosis at all was seen by many as an attack on their identity, as a presumptuous attack by psychiatrists on self-determination and development which are protected under the constitutions of many countries.

It is important to remember that in the 1970s, a great deal of pressure was required before the diagnosis transsexualism was included in the DSM-III (American Psychiatric Association, 1980). Self-help organizations, organizations for affected individuals, and professional associations which supported transsexualism hardly existed then nor was there the global networking of interest groups and individuals on the Internet which we have today. It was only a few practitioners who, partly following pressure from their patients, wanted to open up the way, via recognized diagnosis, to the then still very controversial treatment options of hormonal and surgical reassignment. They in fact succeeded in doing so.

Interestingly, there are currently again two groups making every effort to be included in the DSM-5. The first group consists of men who seek castration and who go by the name *Male to Eunuch* (Roberts, Brett, Johnson, & Wassersug, 2008; Vale et al., 2010; Wassersug & Johnson, 2007). The second group are those people who wish to have other body parts or functions either amputated or shut down, arguing that only in this way they can live a reasonably fulfilled life, a phenomenon known by the not yet formally adopted diagnosis of *Body Integrity Identity Disorder* (BIID), an identity disorder referring to physical integrity (First, 2005; First & Fisher, 2012; Stirn, Thiel, & Oddo, 2009). For example, an adult man contacted the author demanding a high transverse lesion. He was indulging himself with the thought of how satisfying life as a paraplegic confined to a wheelchair would be for him. Another man, already a pensioner, wanted to have one of his legs amputated explaining that this had been his greatest wish since he was a child. Only then could he feel "whole."

A doctor giving in to such demands is liable to punishment by law in many countries for causing grievous bodily harm. This also used to apply to the now so common sex reassignment operations. Therefore, it is of considerable importance whether a request for these procedures is part of a recognized diagnosis or not.

In the DSM-5, the former diagnosis *Gender Identity Disorder* has been replaced by the diagnosis *Gender Dysphoria*. In defining the diagnosis and its symptoms, the term identity still plays a major role. That is why it seems worthwhile to have a closer look at the history of the rather young term identity, its variations in different contexts, and its philosophical, psychological, and political connotations.

17.2 The History of the Term Identity

17.2.1 Philosophical Tradition

In philosophical tradition, identity can be defined as the connectedness of the general and the individual, i.e., as sameness under discontinuous conditions. If we are talking in terms of identity, then nonidentity, otherness, and the disparate are in striking contrast. We usually only have to think about identity when it is no longer assumed, but questioned.

How long have people actually been talking about identity? It is for a remarkably short time. In the tenth volume of Jacob and Wilhelm Grimm's German Dictionary (33 large volumes, published between 1854 and 1971) which deals with the letters H to J, first published only 135 years ago in 1877, the word identity is not even mentioned. This allows for the assumption that at this time there was still no word in everyday language for what we now call identity. At best, identity was an expression used in specialist circles only. Indeed, the concept of identity played a central role in the work of the philosopher and romantic writer Friedrich Schelling. In *Representation of My System of Philosophy* (Schelling, 1801; 2004), he first conceptualized his *system of absolute identity*, which he further developed in later works (Sandkühler, 1976; Zeltner, 1976). With this work he laid the foundation for identity to become a *central epistemological concept* of the modern history of philosophy, which will, however, not be further discussed here apart from the three following examples for the purpose of illustration.

First, an easily comprehensible example taken from the history of theology shows that the philosophical question of how identity can be maintained in the discontinuity of historical developments is much older than the psychological question of the identity of individuals. For Jewish theology, it is important to clarify how the people of Israel managed to maintain their identity through the vicissitudes of their political organization first as nomads, then as slaves in Egypt, then as an organized community as a city-state in Jerusalem under the rule of King David, and later scattered in the Diaspora. For Christian theology, on the other hand, even after the break with Jewish theology, it was important to outline the continuity of its history of salvation from its beginning, creation, up to the current situation, thus bridging the many breaks in this development. From this search for identity, a separate branch of theology has grown, so-called history of traditions, in which the sameness of belief under discontinuous conditions is asserted.

The second example comes from Oskar Negt and Alexander Kluge's (1981) book *Geschichte und Eigensinn* ("History and Self-Will"). This book can be read as a collection of material which can be used to help establish what was possibly understood by *German identity* in postwar Germany. The book states that

> …as long as we are dealing with identity, we are talking about a chain of characteristics which finds itself in a condition of radical needs, i.e., as far as the substance is concerned about non-identity.
>
> Radical attempts at identity cost life [Kleist] or parts of communication [Hölderlin].
>
> Always when national and German [identity] are strongly discussed, we are dealing with a deficit.

This is an interesting statement, which—expressed more generally—might also alert clinicians to pay attention: always when identity is strongly discussed, we may be dealing with a deficit.

Kluge and Negt are looking for the connection between, or rather the identity of, the general and the individual. They quote Theodor Fontane's (1899) political novel *Der Stechlin* stating that

> …our whole society (and especially that particular class which specifically uses that word to designate itself) is built around the ego. Therein lies its curse and that's what is going to destroy it.

While Stechlin's red rooster seismographically announces the connection between the general and the individual, the characters described by Fontane are left at most with a longing for an identity of the general and the individual. It is only a "stupid lake," the Stechlin, that has a mimetic connection to the whole world, not, on the other hand, humans. Here we can find confirmation of the argument that identity must always be claimed where it is not itself naturally present. With the term identity, a sameness is claimed which either in the very moment of description is already overtaken by discontinuity or which is eschatologically projected into the future.

The third example may be found in the pioneering book of the Nobel prize winner Amartya Sen (2006) *Identity and Violence*. *The Illusion of Destiny*. He discusses the shortcomings of the present debate about the clash of cultures and the abusive referral to cultural and religious identities within this context. The German translation of his book has the following different title: *The Identity Trap. Why There Is No War of Cultures* (Die Identitätsfalle. Warum es keinen Krieg der Kulturen gibt). Sen's metaphor of identity as a trap is noteworthy for the purposes of this chapter.

17.2.2 Social Psychological Tradition

The social psychological term of personal identity (Dubiel, 1976) evolved theoretically from the unresolved problems of role theory which, within the tight framework of their basic assumptions, was unable to answer many questions, such as the question of how a person integrates the numerous roles expected of him into a differentiated, but still consistent, ego. Nowhere in Sigmund Freud's work is the term ego-identity used in a theoretically relevant way, but the personality model developed by him has inspired many sociological and sociopsychological identity theories, above all Talcott Parsons (1968) socialization theory and Erik Homburger Erikson's (1970) psychoanalytically oriented concept of *Identity and the Life Cycle*. In the socialization process, the individual must overcome a series of psychosocial crises which are phase-specifically accentuated and which are accompanied by the acquisition and rejection of identifications with primary significant persons. Ego-identity is defined by Erikson as the

> *conviction …, that* the ego *is learning effective steps toward a tangible* collective future*, that it is developing into a defined* ego *within a social reality* (Erikson, 1970).

According to Erikson, ego-identity can only be ascribed to a person after adolescence, and it means that this person experiences himself on the one hand as a unique individual (personal identity, self-likeness, and continuity of the person in time) while, on the other hand and at the same time, as belonging to a particular social group (group identity, constancy of the symbols of a group despite fluctuations in group membership), finally finding his place in this group and experiencing acceptance. It seems to be particularly important to refer to this interactive aspect inherent to identity, as it contributes to the explanation of the vast range of identities being discussed today, addressed further below.

Regardless of diverse critical commentary and individual modifications, in psychoanalysis and psychotherapy, Erikson's concepts have found extremely wide prevalence and recognition, and they have continued to prove useful as a heuristic model in concrete psychotherapeutic work. (For further theory construction on ego-identity in social psychology and philosophy, see Goffman, 1959, 1963; Habermas, 1968; Mead, 1967; Strauss, 1959, and for further theory construction on collective identity, see Niethammer, 2000).

The following terms contribute toward the development of individual identity. Each of these terms has a history and various interpretations, mainly in social psychology and psychoanalysis, which would require independent papers to describe them. As the general theme of identity here will only be discussed as a precursor to and understanding of gender and sexual identity, the brief descriptions below should suffice. Some of these terms refer to preverbally occurring processes, others to unconscious processes, and again others to processes which can become conscious (for full details, see Laplanche & Pontalis, 1998). I added "sexual experiences" to the terms referred to by these authors, as they are of considerable importance for our discussion here.

Primary identification: Primitive subject formation following the lead of others closely connected with oral assimilation. Object cathexis and identification are not yet differentiated.

Imitation: Primary modus for the preservation of object constancy serving to protect against separation anxiety, preverbally, in essence: if I behave like my mother, she will be with me.

Introjection: The subject allows objects to penetrate his fantasies and their inherent qualities from the outside inwards. The physical model is assimilation; however, introjection does not necessarily imply a reference to physical boundaries, as we also talk of introjection into the ego, into the ego ideal, etc.

Sexual experiences: Both positive and negative sexual experiences can be determining, the latter in the sense of identification with the aggressor.

Identification: Psychological process in which an aspect, a characteristic, an attribute, and also attachment styles of another are assimilated.

Identification with an idealized object: In the sense of I want to be like him/her. Failure here creates envy.

Identification with the aggressor: In the sense of If I am like the person who attacks me, then nothing can happen to me.

Projective identification: The self is either partially or entirely transferred into the other in order to either harm or control him/her.

Counter identification (also disidentifying; Greenson, 1968): In the sense of I do not want to be like him/her. Failure creates shame.

Identification through personification: A largely conscious process, emulation of idols.

Identity creation: Integrative ego performance which goes far beyond individual identifications.

Identity diffusion: Failure of integration necessary for identity creation.

17.3 The History of the Terms Gender Identity and Sexual Identity

If you were to suddenly ask the average person about his identity, he or she would probably react much like the student of physics who was asked in an exam what a vacuum is. Stuttering embarrassedly, he could finally only answer "It's in my head, but I can't really explain what it is just now." Most adults would react in a similar way when asked about their gender identity. They experience themselves as either women or men without ever having thought about their gender identity or being able to give any detailed information on what they understand by it. As long as they are not asked about it, they are sure of their gender identity.

Gender identity and sexual identity have only more recently been under discussion as a subcategory of personal identity. These describe the biographical continuity of an individual as either male or female and now probably also as a third, fourth, or fifth gender of some sort. Ultimately, gender identity only became a term in its own right at the time when both of the basic identities of woman and man were called into question. This can be deduced from the titles of the two major works of Kinsey, Pomeroy, and Martin (1948, 1953), which became the basis of modern sexology after the Second World War. Apart from man and woman, nothing else was then considered. There were only two sexual identities, and this term, along with the expression "gender identity," did not yet require any mention, as what was or might be meant by it was not yet an issue and therefore was not a topic for debate.

By gender identity and sexual identity in the narrower and technical sense of the word, something more specific is implied than the phenomena described in health insurance claims to cover expenses related to psychotherapy for patients not being sure of their female or male identity. Descriptions on these claims usually refer to the crises or threshold situations elaborated by Erikson, such as situations in which a female patient feels overwhelmed by her newly adopted role as wife and mother to the extent that she decompensates depressively in a regressive movement or a male patient who initiates perverse rituals when too much is demanded of him in stressful situations. In terms of Morgenthaler's (1984) sealing function, the perverse staging in the male patient's case serves the stabilization of self and identity without the person questioning his own maleness in general. According to classic neurosis theory, cases of fragile male or female identity involved interior statements assuming that the persons affected did not fundamentally call their femaleness or maleness into question (see Hohage, 2008; Thomä & Kächele, 1987/1992).

The discourse on gender identity arose against a different background. It was above all the work of the sexologist John Money and the psychoanalyst Robert Stoller that paved the way for the establishment of this term in everyday language. Money worked at *Johns Hopkins University Hospital* in Baltimore, Maryland, USA, and was concerned with the psychosexual development of children with chromosomal variations, endocrine disorders, and ambiguous genitalia. In order to be able to differentiate between the genital anatomy on the one hand and the psychosexual identity on the other, he searched for new terminology and definitions and introduced in 1955 the term *gender role* (Money, 1955) and in 1966 the term *gender identity* (Money, 1985, 1994).

Many German-language publications on gender identity and transsexuality explain that in contrast to German, where there is only one word for gender (*Geschlecht*), in British and American English, there are two: "sex" as an indication of the physical findings and "gender" as a category for the description of the psychological findings; in these German publications, it is generally assumed that this has always been the case in English. But in fact, this distinction was altogether uncommon in Britain and

America up to the 1960s, and the now common distinction between sex on the one hand and gender identity on the other in British and American English shows just how quickly the differentiation introduced into academic discourse by Money has been adopted as a layman's term and imposed almost universally.

With the term gender role, Money wanted to characterize

> *what a person says or does to indicate his/her status as boy or man, or girl or woman. It* includes, *but is not restricted to*, sexuality *in the sense of* eroticism (Money, 1994).

He was concerned with describing on a phenomenological level, a unitary instead of a dichotomous phenomenon. By role he understood not something externally imposed.

> *In theatre language, gender role is not simply a piece of paper presented to an* actor *but a* role incorporated *into the* actor, *who, metamorphosed by it, then incorporates it and manifests it in himself* (Money, 1994).

Contrary to Money's intentions, the logic of dichotomization established itself in the mid-1960s. The new term "gender identity" was created. The *Johns Hopkins University Hospital* was the first university clinic to implement so-called sex changes and thus helped this method of treatment for patients with transsexual symptomatology toward worldwide recognition. The team dealing with this was initially unofficially referred to as the Sex Change Clinic. Money insisted upon renaming the institution the Gender Identity Clinic, as he was interested in establishing a center for the treatment of a variety of disorders of gender identity, but although the name was adopted, his broader-based concept was not. The term gender identity was only associated with transsexuality in everyday use and spread like wildfire around the world following the publication of Harry Benjamin's (1966) monograph *The Transsexual Phenomenon*.

Around the same time as Money, Stoller had set up a psychoanalytical gender identity work group at the University of California, from which the *Gender Identity Research Clinic* at the University of California had emerged by the time of publication of Stoller's monograph *Sex and Gender* (Stoller, 1968). With his monograph and its second volume, *The Transsexual Experiment* (Stoller, 1975), as well as with countless other articles, Stoller made a substantial contribution to the spreads of the term gender identity in psychoanalysis and in the social sciences.

Money (1994) regretted the incipient dichotomizing discussion, which led, in his opinion, to gross oversimplifications. Sex and gender were now linguistically conceived as separate categories, with sex being determined as (exclusively) biological and gender, on the other hand, understood as (exclusively) social. The larger part of his life's work was dedicated to overcoming such oversimplifying discussions on nature and nurture. In order to underscore his point, he did not usually write the terms out in full, but used acronyms, abbreviations, or formulae, such as G-I/R (Gender Identity/Role, which he believed to be two sides of the same coin). It was painful for him to watch not only how sex and gender were divided between the natural sciences and the humanities but also how his idea of gender identity was separated from that of gender role. In this trivialization, gender role was henceforth treated as a purely social construction and ultimately as a randomly alterable behavior.

For people with uncertain or “transposed” gender identities, this would have substantial implications on a treatment level, as the dichotomous conceptualization resulted in dichotomous accesses to treatment: if sex was conceived of as the natural base, then psychotherapy had to support the patient in accepting his nature and sex change was anathema; if gender was conceived of as the natural base, then the treatment of choice was sex reassignment as early as possible. Dichotomization was perpetuated among many treatment providers. It has contributed to the well-known controversies about the legitimacy or illegitimacy of so-called sex change operations, controversies which gained momentum in waves from 1950 into the 1980s (Boss, 1950/1951; Burzig, 1982; Mitscherlich, 1950/1951; Mitscherlich, Bally et al. 1950/1951; Mitscherlich, Georgi et al. 1950/1951; Springer, 1981; see further Pfäfflin, 1983, 1993, 1994). In contrast, Money’s ideas were considerably more complex and took into account somatic, psychic, and social influences on the development of gender identity equally (Money, 1994).

Since the 1980s, the discourse on treatment for patients with gender identity concerns has shifted considerably. “Sex change” operations are freely available in many centers around the globe. While once patients and doctors had to fight for the legitimization of such operations, the discourse has now changed radically. Several interest groups of persons affected are now emphatically questioning whether hormonal or surgical “sex change” procedures should still be required at all for a change in their legal sex status or whether it would be sufficient for people, whatever their gender or sexual identity might be, to alter their legal sex status, irrespective of whether they have undergone surgery or not. While once those affected asserted their wishes and emphasized their concern with the frequently very serious threat, “If I don’t get an operation, I’ll kill myself,” today they pursue court action against the need for an operation as a requirement for legal recognition of their new gender assignment. In consequence of this development, the German Federal Constitutional Court ruled on January 11, 2011, that sex reassignment surgery is no longer a prerequisite for a legal sex change, as it used to be according to the regulations of the German Law for Transsexuals of 1980.

17.4 From Singular to Plural: Transgenderism, Neo-Sexualities, and Sexual Identities

Traditionally, the identity of a person was referred to in the singular; plural identities of one individual person only appeared in psychoanalytical literature at the end of the 1950s in the work of Phyllis Greenacre (1971), without this being taken up more widely at that time. Further developments in the discourse on transsexualism and transgenderism were needed for further changes in this respect.

17.4.1 Trans-Pluralities

The link between both positions (i.e., sex change operations have to be fought for in court vs. even without hormonal treatment and sex reassignment surgery, a change in legal sex must be possible at any time) can be found in the discourse on *transgenderism*. It comes from a background which has long discarded the dialectic integration of disposition and environment (or, in Money's words, *nature and nurture*) and has opted for a purely constructivist explanation of gender identity. The first person to term herself *transgenderist* was very probably Virginia Prince in the late 1970s or early 1980s. She was the protagonist of self-help movements in the USA devoted to living in the female gender role without wishing to avail themselves of the medical treatment model for transsexuals.

In January 1986, the sociologist Richard Ekins founded a *Trans-Gender Archive* at the University of Ulster in Northern Ireland. He used this term following Virginia Prince's self-description as transgenderist and does not recall having encountered the term previously in the literature or elsewhere (pers. communication, Richard Ekins 1997). At that time still a psychoanalytical trainee, he hyphenated the term in its written form, consistent with the tradition of the *British Psycho-Analytic Society*, where a long discussion on the correct English spelling of the term psychoanalysis was being held at the time of Strachey's translation of Freud's works, after Strachey had written the word psychoanalysis with a hyphen. In order to gain material for his archive, Ekins published his explicitly constructivist approach to research in the publications of transvestite and transsexual organizations in England. Without his knowledge, these texts were reprinted in corresponding publications in the USA but there written without a hyphen. It is that spelling of the word *transgender* that has now found widespread acceptance.

The terminological shift in emphasis from transsexualism to transgenderism was a first step toward further differentiation in the description of related phenomena documented with great precision by Ekins and King (2006)). If the first transsexuals were exclusively and emphatically concerned with being *transformed* from woman to man or man to woman (in terms of role, physical changes, and legal recognition), the first transgenderists' lives oscillated between variably long phases of life in either the one or the other gender role. In the 1980s and 1990s, numerous ethnological and culture-comparative studies were published which showed that there were many other variants (see the overview in Cohen-Kettenis & Pfäfflin, 2003). Western culture can also be understood as a diverse ethnological setting in which new types are always appearing (e.g., the culture of *Shemales*, males who choose to feminize themselves hormonally and through facial and breast surgery but who want to keep their original genitals [Phillips, 2006]). Soon further groups began to fundamentally *negate* the gender dichotomy. They called themselves *Pomosexuals* (Queen & Schimel, 1997) and *GenderQueer* (Nestle, Howell, & Wilchins, 2002).

One additional type developed which wanted to separate itself completely from the concept of gender, producing and propagating every possible lifestyle to escape gender. Ekins and King termed this process *transcending*, which can be best defined as the desire to overcome the gender question and leave it behind. Followers of this movement state that they no longer have any interest in whether they are called man, woman, transgender, transman, transwoman, just trans, or even simply *per* (from person). They claim to manage without any of these labels and require no diagnosis for their preferred lifestyles. However, at the same time, they demand on principle to be able to take advantage of every available treatment. In terms of the remarks made by Negt and Kluge (1981) cited above, they declare their identity to be ultimately not definable and negate it. Thus, their identity can be seen as emerging in the guise of a nonidentity.

Against the background of Erikson's concept of identity, the issue is no longer whether one belongs to a group in which one wishes to find one's place, but instead the issue is about the delimitation of such groups. Belonging to a transsexual group is perceived as excessively restrictive; a transgender group is founded and is, however, also experienced as restrictive, then a trans-group, a per-group, and so on. Thus, one's own sexual identity or one's own gender is characterized ultimately by detaching oneself from all group affiliations. The ultimate outcome is that there are as many sexual/gender identities as there are people.

17.4.2 Sexuality and Identity Pluralities

In the 1970s, initially in parts of sociological and sexological literature, *sexualities* as opposed to sexuality in the singular were beginning to be discussed, as John Gagnon, a sociologist and psychologist teaching at New York State University in Stony Brook, programmatically did in his textbook *Human Sexualities* (Gagnon, 1977; compare Simon, 1996). Gradually, this plural term became more commonly used, and it was not until 1998 that a professional journal with the title *Sexualities* appeared on the market (Plummer, 1998).

It appears that *transsexualism a*nd *transgenderism* were the first of the sexualities Sigusch (2005) included in his anthology under the heading of *neo-sexualities*. He chose this title following words such as neocortex, neoplasm, or neocolonialism, as he thought that the "neo-sexual revolution," in his view, "had arisen over two or three decades from the neo-sexualities" and was indeed something new, opening up "new freedoms," whilst at the same time installing "new constraints." Never before, he stated, had sexual freedom been as great as now. The people who benefited from this new freedom were those "who themselves had been regarded after the sexual revolution of the 20th century as abnormal, sick, perverse, and morally corrupt." However, "the more incessant and intrusive the sexual" is, "publicly inserted and commercialized," the more its explosive force will also diminish, and the more banal it will become. Sexuality is "today no longer the metaphor of pleasure, of intoxication, of revolution, of progress and of happiness."

It is remarkable that Sigusch does not speak of sexual identities, but rather of sexualities and neo-sexualities, which he rightly characterizes as new phenomena, while at the same time emphasizing their fleeting and ever-changing phenomenology. In her recent book *Gender Circuits. Bodies and Identities in a Technological Age*, the sociologist Eve Shapiro (2010) goes significantly further in this regard: without further ado, sexualities and neo-sexualities become continually changing identities, including those of transmen who bear children and transwomen who can produce children with sperm frozen before their transformation.

Finally, phenomena which used to be classified as sexual preferences and orientations now present themselves as identities, for example, as gay, lesbian, bisexual, sadomasochistic, pedophile, and even asexual, to name but a few. Detached from every sort of group membership, sexual identity finally becomes a solipsistic project.

17.5 Conclusion

In order to understand these changes, a remarkable article by Reimut Reiche (1997) with the provocative title *Gender Without Sex* is useful. In this article, Reiche addressed the new gender terminology and the underlying semantic change of the word *gender*, focusing in particular on the psychoanalytical and feminist debates. Referring back to the genesis of the acronym *G-I/R* presented by Money, Reiche underscored that *gender* lives from the strength with which it rejects *sex*. In the meantime, the strength of this rejection has been forgotten, which Reiche argues is well documented in the works of Judith Butler (1990, 1993), Judith Kestenberg (1968, 1971), Otto Kernberg (1995), Wolfgang Mertens (1992), Robert Stoller (1968, 1975), and others. *Gender* purified of *sex* has become the primary metaphor (*gender studies*, *gender movement*), having displaced the old psychoanalytical primary metaphor of instinct, along with Freud's concept of bisexuality. Because all gender differences are now supposedly only constructed, there appear to be no longer any natural ones. While Freud's concept of bisexuality is sufficiently open to be able to leave the path of deterministic biology and comply with the construction of gender, the gender discourse pays homage to the illusionary desire for conflict-free sexuality at the cost of repression of sexuality. One could add that it thereby forfeits its material basis and becomes empty and meaningless. Indeed, Niethammer (2000) already called the term *collective identity* a "plastic word."

One does not need to be an adherent of psychoanalysis and its theory of instincts to recognize that the desire for conflict-free sexuality will never be achieved, no more than the desire for a conflict-free identity, whether it is a sexual or any other type of identity. It will never be achieved regardless of any ontologizing of gender differences common in the early days of the feminist debate and the beginning of gender studies before these differences were challenged by deconstructive concepts (Hörisch, 2010). The never-ending efforts toward discovering biological and neurobiological causes for the many expressions of the sexual are rooted in such unrealistic desires and are ultimately attempts to assess the ontologizing of (gender) differences (see further Gender Identity Research and Education Society, 2006a, 2006b; Green, 2006; Pfäfflin, 2006; Zucker, 2006).

Identity constitutes itself as sameness and continuity in the face of continuous discontinuity in an individual's life and in the life of groups. Against the background of the rapidly changing forms of expression of the sexual over the last three decades, the desire to stabilize these vicissitudes by explaining that they are a matter of identities is understandable, in line with what Oskar Negt and Alexander Kluge (1981) had stated:

> In as far as we are dealing with identity, we are talking about a chain of characteristics which finds itself in a state of radical need, i.e., in substance: about non-identity" and, analogously, "always when [identity] is strongly discussed, we are talking about a deficit.

This may well be the background to why it is so important now to some groups to have sexual/gender identity (which is also a partial identity, the durability of which can certainly be questioned) incorporated into the anti-discrimination article of the constitution of their country, as was recently proposed by some activists in Germany. In my view, this is superfluous, as what is sought here is already clearly expressed in art. 8 para. 1 and art. 14 of the European Convention on Human Rights (ECHR), as well as in art. 1 para 1 and art. 3 para. 1 of the German constitution. Article 8 of the ECHR protects both private and family life, similarly to art. 3 para. 1 of the German constitution; art. 14 of the ECHR contains a ban on discrimination, including sex/gender-based discrimination. Indeed, supported by these regulations, the European Court of Human Rights in Strasbourg ruled against France and the United Kingdom, two states which had long denied transsexuals and transgenderists full change of legal sex (see further International Commission on Civil Status, 2000 and the *Gender Recognition Act* of the United Kingdom, July 2004). The personal rights guaranteed under the German constitution and the ECHR, and the concept of sex/gender associated with the principle of nondiscrimination established in both sets of regulations, are broadly defined and include sexual as well as gender identity so that there is no necessity of specifically citing the latter. Moreover, the concept of sexual/gender identity is much too vague and fleeting and, as argued above, is at present experiencing a continuous extension in the direction of *all* possible sexual preferences, to be able to ensure better protection of human rights by its inclusion in the constitution. The introduction of the term sexual/gender identity would probably contribute more to confusion than to clarification and increased legal certainty.

Aside from the issue of including sexual/gender identity in anti-discrimination legislation, the new version of the criteria of the DSM-5 diagnosis of *Gender Dysphoria*, insofar as more than just the two traditional sexes/genders of male and female are considered, is to be designated purely descriptively as gender incongruence or *Gender Dysphoria* without the addition of the word *Disorder*. It will be crucial whether one incongruently experiences his/her gender or sexual/gender identity as different from the gender assigned to him/her at birth, and it is left open which other gender he or she may feel that they belong to. *Gender* is consistently talked about and—apart from the somatic intersex forms—there is no longer any distinction made between *sex* and *gender*. Instead of the desire to be counted as belonging to *the other gender*, DSM-5 formulates, to belong to *some other gender*. Anyone developing a need for treatment from such a constellation, not necessarily but certainly potentially, should then be able to receive it.

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